[0826] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

[0827] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[0828] Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial

antibodies), cardiotomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[0829] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0830] In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0831] In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0832] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention

[0833] In preferred embodiments, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a immunosuppressive agent(s).

[0834] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the

pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

[0835] Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[0836] Additionally, polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

[0837] Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1.), respiratory disorders (e.g., asthma and allergy);

gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

[0838] Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chorditis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myosititis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

[0839] In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or

chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

[0840] In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

[0841] Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

[0842] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

[0843] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of:

AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

[0844] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

[0845] In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae, Mycobacterium leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

[0846] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

[0847] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat

infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

[0848] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

[0849] In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

[0850] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

[0851] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.

[0852] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[0853] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.

[0854] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.

[0855] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

[0856] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

[0857] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

[0858] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[0859] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

[0860] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment,

polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

[0861] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[0862] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

[0863] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodificiency.

[0864] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the pretreatment of bone marrow samples prior to transplant.

[0865] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

[0866] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[0867] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

[0868] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications decribed herein, as they may apply to veterinary medicine.

[0869] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

[0870] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

[0871] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

[0872] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

[0873] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory

and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

[0874] The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

[0875] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.

[0876] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

[0877] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

[0878] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).

[0879] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

[0880] In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent

bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carnii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

[0881] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

[0882] In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

[0883] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

[0884] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

[0885] In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

[0886] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the

present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

[0887] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741). Administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention to such animals is useful for the generation of monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention.

Blood-Related Disorders

[0888] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

[0889] In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extrcorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[0890] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 3, column 2 (Library Code).

[0891] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes

(B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

[0892] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

[0893] Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary siderob;astic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune helolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyldopa, dapsone, and/or sulfadrugs. Additionally, rhe polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

[0894] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin

abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

[0895] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thromboasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophelia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorhhagic Telangiectsia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

[0896] The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

[0897] Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

[0898] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing,

preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leokocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

[0899] Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

[0900] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating

lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndome, severe combined immunodeficiency, ataxia telangiectsia).

[0901] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

[0902] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

[0903] In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphpblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukenia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

[0904] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

[0905] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myelod metaplasia, thrombocythemia, (including both primary and seconday thrombocythemia) and chronic myelocytic leukemia.

[0906] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

[0907] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosionophils and macrophages.

[0908] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

[0909] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

[0910] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

Hyperproliferative Disorders

[0911] In certain embodiments, polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through

direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

[0912] For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

[0913] Examples of hyperproliferative disorders that can be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[0914] Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease,

Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis

Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0915] In another preferred embodiment, polynucleotides or polypeptides, or agonists or antagonists of the present invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

[0916] Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

[0917] Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

[0918] Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriodigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertebral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous

dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

[0919] Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

[0920] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 3, column 2 (Library Code).

[0921] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

[0922] Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis,

Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0923] In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

[0924] Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0925] Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

[0926] Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[0927] Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0928] Another preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

[0929] Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

[0930] Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the poynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

[0931] Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

[0932] For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may

be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

[0933] The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

[0934] By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

[0935] Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

[0936] The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0937] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0938] In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

[0939] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

[0940] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragements thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragements thereof. Preferred binding affinities include those with a dissociation constant or Kd less than $5X10^{-6}M$, $10^{-6}M$, $5X10^{-7}M$, $10^{-7}M$, $5X10^{-8}M$, $10^{-8}M$, $5X10^{-9}M$, $10^{-9}M$, $5X10^{-10}M$, $10^{-10}M$, $5X10^{-11}M$, $10^{-11}M$, $5X10^{-12}M$, $10^{-12}M$, $5X10^{-13}M$, $10^{-13}M$, $5X10^{-14}M$, $10^{-14}M$, $5X10^{-15}M$, and $10^{-15}M$.

[0941] Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

[0942] Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuviants, such as apoptonin, galectins, thioredoxins, anti-inflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

[0943] Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such

thereapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

[0944] In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodes associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodes of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

[0945] Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

<u>Renal Disorders</u>

[0946] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the renal system. Renal disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

[0947] Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic

glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis), and kidney disorders resulting form urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

[0948] In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or treat metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

[0949] Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (e.g., glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

[0950] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators,

gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Cardiovascular Disorders

[0951] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

[0952] Cardiovascular disorders include, but are not limited to, cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include, but are not limited to, aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

[0953] Cardiovascular disorders also include, but are not limited to, heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

[0954] Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

[0955] Heart valve diseases include, but are not limited to, aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

[0956] Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

[0957] Myocardial ischemias include, but are not limited to, coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

[0958] Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia

telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

[0959] Aneurysms include, but are not limited to, dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

[0960] Arterial occlusive diseases include, but are not limited to, arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

[0961] Cerebrovascular disorders include, but are not limited to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

[0962] Embolisms include, but are not limited to, air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include, but are not limited to, coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

[0963] Ischemic disorders include, but are not limited to, cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes, but is not limited to, aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

[0964] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral

or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Respiratory Disorders

[0965] Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

[0966] Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumoncoccal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).

[0967] Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis), fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in

people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia* spp.), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthsma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

Anti-Angiogenesis Activity

[0968] The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al., Cell 56*:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of

eye disorders, and psoriasis. See, e.g., reviews by Moses *et al., Biotech.* *9*:630-634 (1991); Folkman *et al., N. Engl. J. Med., 333*:1757-1763 (1995); Auerbach *et al., J. Microvasc. Res. 29*:401-411 (1985); Folkman, Advances in Cancer Research, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Opthalmol. 94*:715-743 (1982); and Folkman *et al.,* Science *221*:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science 235*:442-447 (1987).

[0969] The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.,* Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)).Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non- small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

[0970] Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists

may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

[0971] Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

[0972] For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

[0973] Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

[0974] Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al., Am. J. Ophthal. 85*:704-710 (1978) and Gartner *et al., Surv. Ophthal. 22*:291-312 (1978).

[0975] Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

[0976] Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a

high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

[0977] Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

[0978] Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

[0979] Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist

and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

[0980] Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreous injection and/or via intraocular implants.

[0981] Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

[0982] Moreover, disorders and/or states, which can be treated, prevented, diagnosed, and/or prognosed with the the polynucleotides, polypeptides, agonists and/or agonists of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

[0983] In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning

after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

[0984] Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

[0985] Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

[0986] Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

[0987] Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of

tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

[0988] The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0989] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0990] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0991] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable

tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0992] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

Diseases at the Cellular Level

[0993] Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's

disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0994] In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

[0995] Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0996] Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognesed using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include, but are not limited to, AIDS;

neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

[0997] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

[0998] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts,

autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

[0999] It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

[1000] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

[1001] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or

antagonists of the present invention, could also be used to treat gastric and doudenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

[1002] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

[1003] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic

substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

[1004] In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Neural Activity and Neurological Diseases

[1005] The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in

which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

[1006] In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

[1007] In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

[1008] In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

[1009] The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, *10*:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, *70*:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, *4*:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

[1010] In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar

palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

[1011] Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

[1012] Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

[1013] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides,

polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

[1014] Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

[1015] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

[1016] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as

Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

[1017] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

[1018] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningtitis such as viral meningtitis which includes lymphocytic choriomeningitis, Bacterial meningtitis which includes Haemophilus Meningtitis, Listeria Meningtitis, Meningococcal Meningtitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningtitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningtitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-

Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

[1019] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sceloris which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

[1020] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-

Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyloclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager

Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia,Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

[1021] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Endocrine Disorders

[1022] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.

[1023] Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to

respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

[1000] Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

[1001] Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

[1002] In specific embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists of those polypeptides (including antibodies) as well as fragments and variants of those polynucleotides, polypeptides, agonists and antagonists, may be used to diagnose, prognose, treat, prevent, or ameliorate

diseases and disorders associated with aberrant glucose metabolism or glucose uptake into cells.

[1003] In a specific embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type I diabetes mellitus (insulin dependent diabetes mellitus, IDDM).

[1004] In another embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type II diabetes mellitus (insulin resistant diabetes mellitus).

[1005] Additionally, in other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or antagonists thereof (especially neutralizing or antagonistic antibodies) may be used to diagnose, prognose, treat, prevent, or ameliorate conditions associated with (type I or type II) diabetes mellitus, including, but not limited to, diabetic ketoacidosis, diabetic coma, nonketotic hyperglycemic-hyperosmolar coma, seizures, mental confusion, drowsiness, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section), dyslipidemia, kidney disease (e.g., renal failure, nephropathy other diseases and disorders as described in the "Renal Disorders" section), nerve damage, neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture.

[1006] In other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to regulate the animal's weight. In specific embodiments the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin..In still other embodiments the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most

preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin-like growth factor.

[1007] In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

[1008] Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

[1009] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 3, column 2 (Library Code).

Reproductive System Disorders

[1010] The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

[1011] Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular

torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

[1012] Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

[1013] Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid paplosis, giant condyloma of Buscke-Lowenstein, and varrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

[1014] Moreover, diseases and/or disorders of the vas deferens include vasculititis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

[1015] Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes

mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

[1016] Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

[1017] Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, keiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelfus, and T-shaped uterus.

[1018] Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

[1019] Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

[1020] Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus eryematosis, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders,and obstruction of the intestine.

[1021] Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

[1022] Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

[1023] Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the polynucleotides, polypeptides, and agonists or antagonists of the present invention include, for example, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

Infectious Disease

[1024] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

[1025] Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta),

Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

[1026] Similarly, bacterial and fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacteria, bacterial families, and fungi: Actinomyces (e.g., Norcardia), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthrasis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candidia, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium dificile*, *Clostridium perfringens*, *Clostridium tetani*), Coccidioides, Corynebacterium (e.g., *Corynebacterium diptheriae*), Cryptococcus, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacter (e.g. *Enterobacter aerogenes*), Enterobacteriaceae (Klebsiella, Salmonella (e.g., *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella typhi*), Serratia, Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g., *Haemophilus influenza* type B), Helicobacter, Legionella (e.g., *Legionella pneumophila*), Leptospira, Listeria (e.g., *Listeria monocytogenes*), Mycoplasma, Mycobacterium (e.g., *Mycobacterium leprae and Mycobacterium tuberculosis)*, Vibrio (e.g., *Vibrio cholerae)*, Neisseriaceae (e.g., *Neisseria gonorrhea, Neisseria meningitidis*), Pasteurellacea, Proteus, Pseudomonas (e.g., *Pseudomonas aeruginosa*), Rickettsiaceae, Spirochetes (e.g., Treponema spp., Leptospira spp., Borrelia spp.), Shigella spp., Staphylococcus (e.g., *Staphylococcus aureus*), Meningiococcus, Pneumococcus and Streptococcus (e.g.,

Streptococcus pneumoniae and Groups A, B, and C Streptococci), and Ureaplasmas. These bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye infections (e.g., conjunctivitis), uveitis, tuberculosis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, Legionella disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., mengitis types A and B), chlamydia, syphillis, diphtheria, leprosy, brucellosis, peptic ulcers, anthrax, spontaneous abortions, birth defects, pneumonia, lung infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory diseases, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections, noscomial infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, diptheria, botulism, and/or meningitis type B.

[1027] Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardias, Helminthiasis, Leishmaniasis, Schistisoma, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparium*, *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat, prevent, and/or diagnose any of these

symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose malaria.

[1028] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

[1029] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

[1030] Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

[1031] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

[1032] Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Gastrointestinal Disorders

[1033] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowl lymphoma)), and ulcers, such as peptic ulcers.

[1034] Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperioneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess,).

[1035] Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum,

Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata, Echinococcus granulosus, Diphyllobothrium spp.*, and *T. solium*).

[1036] Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma,

cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Karposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

[1037] Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

[1038] Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

[1039] Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoin neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption

syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowl syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

[1040] Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

Chemotaxis

[1041] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

[1042] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

[1043] It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

[1044] A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors),or small molecules.

[1045] Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the

polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

[1046] Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

[1047] The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

[1048] Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

[1049] Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

[1050] Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labeled. The polypeptides can be labeled by a

variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

[1051] Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

[1052] As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

[1053] Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al., Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al., J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous

molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

[1054] Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[1055] Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and ^{3}[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of ^{3}[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of ^{3}[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

[1056] In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential

agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

[1057] All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

[1058] Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

[1059] In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

[1060] As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[1061] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

[1062] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

[1063] Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

[1064] This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located

intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

[1065] Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

[1066] Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

[1067] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Antisense And Ribozyme (Antagonists)

[1068] In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to cDNA sequences contained in cDNA plasmid:Z identified for example, in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

[1069] For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for *in vivo* use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5 end and a HindIII site on the 3 end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl2, 10MM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

[1070] For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA

oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into receptor polypeptide.

[1071] In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells.. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, et al., Nature 296:39-42 (1982)), etc.

[1072] The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

[1073] Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most

efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

[1074] The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

[1075] The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine,

5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

[1076] The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

[1077] In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

[1078] In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

[1079] Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

[1080] While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

[1081] Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

[1082] As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g., for improved stability, targeting, etc.) and should be delivered to cells which express *in vivo*. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

[1083] Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

[1084] The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract

surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

[1085] The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

[1086] The antagonist/agonist may also be employed to treat the diseases described herein.

[1087] Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

Binding Peptides and Other Molecules

[1088] The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

[1089] This method comprises the steps of:

1. contacting polypeptides of the invention with a plurality of molecules; and
2. identifying a molecule that binds the polypeptides of the invention.

[1090] The step of contacting the polypeptides of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the polypeptides on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptides. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized polypeptides of the invention. The molecules having a selective affinity for the polypeptides can then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptides to the solid support, solvent, and conditions of

the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

[1091] Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by the polypeptides of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptides and the individual clone. Prior to contacting the polypeptides with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for polypeptides of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptides of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

[1092] In certain situations, it may be desirable to wash away any unbound polypeptides from a mixture of the polypeptides of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the polypeptides of the invention or the plurality of polypeptides are bound to a solid support.

[1093] The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind polypeptides of the

invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; Medynski, 1994, Bio/Technology 12:709-710;Gallop et al., 1994, J. Medicinal Chemistry 37(9):1233-1251; Ohlmeyer et al., 1993, Proc. Natl. Acad. Sci. USA 90:10922-10926; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422-11426; Houghten et al., 1992, Biotechniques 13:412; Jayawickreme et al., 1994, Proc. Natl. Acad. Sci. USA 91:1614-1618; Salmon et al., 1993, Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383.

[1094] Examples of phage display libraries are described in Scott and Smith, 1990, Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718); Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

[1095] In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

[1096] By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

[1097] The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

[1098] Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple

scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

[1099] Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

[1100] Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992; BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al., 1994, Cell 76:933-945; Staudt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94/18318.

[1101] In a specific embodiment, screening to identify a molecule that binds polypeptides of the invention can be carried out by contacting the library members with polypeptides of the invention immobilized on a solid phase and harvesting those library members that bind to the polypeptides of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

[1102] In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to polypeptides of the invention.

[1103] Where the binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

[1104] Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

[1105] As mentioned above, in the case of a binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

[1106] The selected binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Other Activities

[1107] A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

[1108] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue

repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

[1109] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

[1110] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

[1111] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

[1112] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

[1113] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

[1114] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of

the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

[1115] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to treat weight disorders, including but not limited to, obesity, cachexia, wasting disease, anorexia, and bulimia.

[1116] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

[1117] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

[1118] The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Other Preferred Embodiments

[1119] Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or cDNA plasmid:V.

[1120] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions identified for SEQ ID NO:X in Table 1.

[1121] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or cDNA plasmid:V.

[1122] Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or cDNA plasmid:V.

[1123] A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X in the range of positions identified for SEQ ID NO:X in Table 1.

[1124] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or cDNA plasmid:V.

[1125] Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto and/or cDNA plasmid:V, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

[1126] Also preferred is a composition of matter comprising a DNA molecule which comprises cDNA plasmid:V.

[1127] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of cDNA plasmid:V.

[1128] Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by cDNA plasmid:V.

[1129] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by cDNA plasmid:V.

[1130] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by cDNA plasmid:V.

[1131] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by cDNA plasmid:V.

[1132] A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto and a nucleotide sequence encoded by cDNA plasmid:V; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

[1133] Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

[1134] A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto and a nucleotide sequence encoded by cDNA plasmid:V.

[1135] The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

[1136] Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto or cDNA plasmid:V which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto and a nucleotide sequence of cDNA plasmid:V.

[1137] The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

[1138] Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto and a nucleotide sequence encoded by cDNA plasmid:V. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

[1139] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and/or a polypeptide encoded by cDNA plasmid:V.

[1140] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and/or a polypeptide encoded by cDNA plasmid:V.

[1141] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and/or a polypeptide encoded by cDNA plasmid:V.

[1142] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and/or a polypeptide encoded by cDNA plasmid:V.

[1143] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by cDNA plasmid:V.

[1144] Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded by cDNA plasmid:V; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and/or the polypeptide sequence of SEQ ID NO:Y.

[1145] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by cDNA plasmid:V.

[1146] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a polypeptide encoded by cDNA plasmid:V.

[1147] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by cDNA plasmid:V.

[1148] Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[1149] Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining

whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

[1150] Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[1151] Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

[1152] Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[1153] Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

[1154] Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous

amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[1155] In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

[1156] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[1157] Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

[1158] Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[1159] Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

[1160] Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V. The isolated polypeptide produced by this method is also preferred.

[1161] Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

[1162] Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

[1163] In specific embodiments of the invention, for each "Contig ID" listed in the fourth column of Table 2, preferably excluded are one or more polynucleotides comprising, or alternatively consisting of, a nucleotide sequence referenced in the fifth column of Table 2 and described by the general formula of a-b, whereas a and b are uniquely determined for the corresponding SEQ ID NO:X referred to in column 3 of Table 2. Further specific embodiments are directed to polynucleotide sequences excluding one, two, three, four, or more of the specific polynucleotide sequences referred to in the fifth column of Table 2.

[1164] Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of c - d, where both c and d correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where d is greater than or equal to c + 14.

[1165] In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby incorporated by reference in their entirety.

TABLE 2

Gene No.	cDNA Plasmid: V	NT SEQ ID NO: X	Contig ID	Public Accession Numbers
1	HCE1P80	2	973903	BG033745, AA476827, AV704156, AL137944, AI971680, AW297211, BF760130, AI520706, BF833782, BE907421, BE242671, AW936474, AW936371, AW190143, AW519008, AI432598, AI393538, AW295856, AA393801, BF687731, AI765546, BF898133, AA146856, BF217337, BE146273, AL532972, AI204615, BF437991, AA146855, AL021453.1, AK026002.1, AL355838.3, AL009047.1, AL354696.11, AL356806.4, AC010460.6, AC010977.4, AC013242.7, AP000426.3, AL512268.10, AC009245.10, AP001001.4, AC022415.5, AC018517.6, AC005521.1, AC008163.2, AL138878.10, AC007881.4, AL136531.16, AL138976.5, AL050350.14, AL160254.10, AC004584.1, AL356379.10, AL158815.14, AL109751.19, AC005384.2, AC008736.6, AC022542.4, AL136160.18, AL591807.1, AL031681. 16.
1	HCE1P80	22	1315876	
1	HCEJP80	23	1055553	
2	HUFGH53	3	1143339	AI672862, AI972278, AI090242, AI365229, AA524422, AI916766, AW242863, AW014261, AA044337, AI863149, AI658700, AI491865, AI344186, BF001214, AI658683, AW972265, AI680049, AI638089, AA044219, AA775576, AA034372, AI023942, AI276995, W25392, AA603067, AA034373, AI197784, W35182, AA339233, H55506, AW084219, AW168373, AA807088, AW151785, AI866798, AI673256, BF817402, AI473598, AI347701, AI799199, AI569309, AI866002, BF885085, BF815196, BG251264, AI474107, AI635367, AI682075, AI828731, AW089179, AW151714, AI633419, BE964767, AI696819, AW189424, AV682807, AW983822, AI491783, AI250848, AI933785, AI365256, AW085786, AI874151, AI932949, AW149869, AW023590, AI873644, AI697324, AI274013, AI539771, BG260144, AV682802, AI308032, AI251830, AI344785, BG058039, AI648502, AW954031, AW088899, AW168485, AI280670, AI590999, AI699011, AW088903, BG027280, BE613727, AI922901, AI922561, AI799195, AW004886, AI620868, AI859464, AI818578, BF921092, AW130863, AI687009, AW152550, AI538342, BF968910, BE963918, AI432736, AI249962, AI446373, AI636619, AW191892, AW129230, AW167238, BF914091, AI860045, AI433976, AW079159, AI619716, AW082060, AI890806, AW087938, AI687065,

				AI539153, AI612759, BE963035, AW151729, BF816785, BF816455, AI867042, BF526861, AI566630, AI280661, BE061389, AI866608, BF814541, AI537617, BE963286, AI919345, AI922577, BF915537, AW834355, AI888621, AI476109, BF915208, BE072233, AI366549, AI636719, AI570966, AI610645, AI434242, BF904180, AI620093, AI811168, AI611743, AW083804, AA830821, AI696626, AI589993, BE964497, BE538466, AW265004, BE393551, AI598061, AI587606, AI677797, AI431909, BE965169, AI811684, AW118518, AI613449, AI254727, AI783861, AW192288, AW002174, N74355, AI520702, AI433021, AI859402, AW149227, AI800138, AI890182, AI628833, BF344652, BF795712, AW168031, AW264029, AW169275, AW167448, AW264727, AW083189, AW193203, AI680498, AI805688, AI953880, AI554427, BE907440, AW172723, BG249582, AI475394, AW169001, AI915576, AI868831, AW847410, AW163823, BF811780, BE928768, AI471548, AI559599, AV755332, AI689571, AI355849, AI860783, AI174394, AW189415, AI680457, AI805769, BF814449, BF920893, AI567351, BF339322, AI863321, AI569328, AI521386, AI371228, AI567243, AI952064, AI554218, AW081255, AI888944, AW198075, AW088134, AW079739, AI812015, AI498579, AI702406, AI470284, AI590686, AI468872, AI382670, AI921734, AL036638, AI802240, AW167918, AI560052, AL110306, AI584140, AI862144, AW085667, BG150947, AI628217, AI520810, AI866786, AI648567, AI400725, BE543089, Y07848.1, AL031186.8, Z95116.1, AL050138.1, BC008983.1, AL137461.1, Y14314.1, AL133645.1, BC006201.1, AL137463.1, AK024538.1, AK026408.1, AK026597.1, AL389939.1, AL133075.1, AL389978.1, AL137705.1, AB060929.1, AK026533.1, AK025349.1, AF218031.1, BC005151.1, AF358829.1, AL137556.1, BC003105.1, BC005678.1, AF091084.1, AK026591.1, AL359618.1, AL162062.1, AK025312.1, U39656.1, X69819.1, AL137300.1, AL080137.1, AB056768.1, AK026504.1, BC005858.1, AK000647.1, AF217987.1, AB048974.1, AF090903.1, AL389982.1, AL136749.1, AL080086.1, AF321617.1, BC003650.1, AK000450.1, AF026816.2, AK026947.1, BC001349.1, AJ242859.1, AF000145.1, BC008365.1, AF081197.1, AF081195.1, AL080060.1, AL137273.1, AL512761.1, AB052200.1, AF125949.1, AB049758.1, AK025383.1, BC006412.1, AL050393.1, BC006133.1, BC009033.1, BC003683.1, BC007355.1, AL133014.1, U80742.1, AL137294.1, AK026532.1,

				BC009341.1, AK000652.1, AL162083.1, AF159141.1, BC002839.1, AB048919.1, BC002343.1, BC006494.1, AB063084.1, AB049848.1, AB019565.1, AL122098.1, AL133104.1, AL133565.1, AL512754.1, BC004370.1, AB056427.1, AB060905.1, AB060211.1, BC007641.1, AL157479.1, BC000316.1, BC003682.1, AK025708.1, AL080074.1, AB055361.1, AL390167.1, AL117649.1, AF162270.1, BC006508.1, BC006164.1, AB063008.1, BC008485.1, AB063079.1, AL080158.1, BC000556.1, BC003687.1, AL442072.1, AF242525.1, S61953.1, AC002467.1, BC008780.1, AL136928.1, AB060912.1, AL122049.1, AK026086.1, AB048964.1, AK026528.1, AF217966.1, AL122050.1, AF218014.1, AL162003.1, AL137271.1, AF177336.1, AL359583.1, AL136844.1, AL133665.1, AL133098.1, AK027182.1, AL512746.1, AK024601.1, AB047801.1, AL133557.1, AB060852.1, AL110221.1, BC006807.1, AK026608.1, AL157431.1, AL133568.1, AL136845.1, AL133113.1, BC008893.1, AL136784.1, AB047887.1, AF225424.1, AB055366.1, AK025491.1, AL136843.1, AL110280.1, AL080127.1, AL050149.1, AF217991.1, AL122093.1, AF003737.1, BC009026.1, AK026057.1, BC005890.1, AL049382.1, BC008417.1, AB063088.1, AK027193.1, AF113222.1, AL137538.1, AB055368.1, AK025524.1, BC009253.1, BC007198.1, AL136799.1, AK026865.1, AF078844.1, AL512718.1, AF219137.1, AK000445.1, AK026642.1, AL049465.1, AK026164.1, AF104032.1, AL133081.1, BC004951.1, AL122111.1, AB060863.1, AK025209.1, AL137648.1, AL162006.1, AK026592.1, AL117585.1, AK025573.1, AL136789.1, BC002342.1, AL353940.1, AF207829.1, AK027116.1, AL117432.1, AL512719.1, AL136790.1, AL050277.1, AL080124.1, AF271350.1, BC008387.1, AL359941.1, AL136622.1, AL133077.1, AK026526.1, AB047615.1, AK025906.1, AK026045.1, AB050534.1, AL353957.1, AK026885.1, L30117.1, AF183393.1, AK027164.1, AB060903.1, AL117440.1, AK026551.1, AL117435.1, AL110222.1, AK000718.1, AK026534.1, AF111112.1, AL162002.1, AK026855.1, AL137429.1, AK027113.1, AL137526.1, L19437.2, BC008070.1, AB055315. 1.
2	HUFGH53	24	894857	AI672862, AI972278, AI090242, AI365229, AA524422, AI916766, AW242863, AW014261, AA044337, AI863149, AI658700, AI491865, AI344186, BF001214, AI658683, AW972265,

				AI680049, AI638089, AA044219, AA775576, AA034372, AI023942, AI276995, W25392, AA603067, AA034373, AI197784, W35182, H55506, AA339233, AL031186.8, Y07848.1, Z95116. 1.
2	HUFGH53	25	1407421	
2	HUFGH53	26	1407330	
2	HUFGH53	27	1407326	
2	HUFGH53	28	1324108	
2	HUFGH53	29	1143314	
2	HUFGH53	30	1124368	
3	HWMMO59	4	1426876	AI634846, BF589994, AI660577, AW873053, BE906672, AI241049, AW008561, BF750885, BE963035, AI280661, BF816455, AW088899, AI446003, AI566630, BF694790, BG120816, AI702073, AI537617, BE061389, AI919345, AI633419, AI610645, BF038804, AI554218, AI866002, BF817402, AI867042, AI539028, BE963918, AI859464, AW083804, AI921386, BF968504, AI674912, AI469811, AI627880, AI636719, AI608676, BF904180, BF726504, AI250663, AI433976, BF815196, AI619716, AI561299, AI612759, AW151729, AI699011, BF811780, BF909758, BE621256, AI364788, AI611743, BF914091, BE613727, AW168485, BF814335, BE968711, BF913616, AW103371, AI697324, AI933785, AI805688, BF915537, BG026746, AI365256, AW079159, AI251830, BE964767, BG058039, AI689175, BE928768, AI635464, BE875407, AW087938, AI366549, AI539153, BF816785, BF726237, AW131954, AW090494, AW834355, BF344652, BE393551, BE964089, BG031664, AI494201, AI610756, AA830821, AI963040, AI679916, AL079794, AW102785, BF814409, BE887861, AI921176, AW084219, AW103886, AI499652, AW082594, AI633306, BE967016, BE897632, BF814541, AI345746, N80094, AW858254, AI251205, BF915208, AV682496, AI868831, AI888953, AI886124, AI655932, AW151785, AV683272, AI431909, BF885085, AV690007, AI828731, BF795712, AI432736, AI687065, AW089179, AI696819, AI783861, BE785868, AI680498, AW192375, AI520809, AI922577, AI799234, AI498579, BE875786, AI696626, AW198075, BE904051, BE072233, AI589993, BE544111, BG179099, AI566507, AI264741, AI952360, BF726603, AI866741, AI680457, AI468872, AI866608, BE963286, AI698401, BE884910, AW079572, AI572418, AW172723, AI400725, AI568870, AI241819, BE964497, BE538466, BF854113, AW029263, AI952920, AW020095, AW103893, AI805638, AI805769, AI963062, AW195957, AI624668, BF342070, BE966388, AW071417, AI628292, AW021588, AW085667, AI801605, AI888429, BG181012, AI885974,

				AI493559, AL041772, AI613017, AI432040, BE964981, AW089258, AI628217, AI866887, AI812015, AW235035, BF910810, AW192226, AW168031, AI474076, AI886022, AI891157, AI249962, AI872914, AW104146, BG171779, BF037484, AW088903, AW151714, AW129230, BE246734, AI471361, AI678443, AI587288, AI696378, AW088134, BE965060, AI598113, AW051107, BF752252, BE964198, AI648502, BF924882, AI590645, AI539771, AA425380, AW082040, AW103195, AW084131, AI677797, BF921092, BF792469, AW117907, AI569616, BE965481, BF910849, BF812933, BF204484, AL110306, AI745713, BF725863, AL119791, AI888621, AL041150, AI888944, BE964512, AW858243, BG030364, BE966947, AI922365, AI274769, AI540850, N74355, AI133489, AI929108, AI648663, BC001349.1, BC003683.1, AK025414.1, AB056427.1, AK025209.1, AK025906.1, AL133104.1, AK000652.1, AL512718.1, AB063100.1, AL389978.1, AK000753.1, AK025383.1, AK026865.1, AK024538.1, AK025958.1, AB063008.1, BC008417.1, AF225424.1, BC003548.1, AB060826.1, AL080124.1, AL137556.1, AB063046.1, AB019565.1, AL122098.1, BC007198.1, BC008893.1, AL080060.1, AK026642.1, BC005678.1, AF104032.1, AL050024.1, AL512719.1, AB050534.1, AK025491.1, AL136928.1, AL512761.1, AK024601.1, AK027116.1, AB049758.1, AL389939.1, AF271350.1, AL050138.1, AL136843.1, U80742.1, AB060214.1, AL137526.1, BC006164.1, U39656.1, X69819.1, AB060929.1, AB056768.1, AL390167.1, AK027868.1, AL512754.1, BC003687.1, AB060863.1, AB063079.1, AK026608.1, AB060839.1, AL117432.1, AF111112.1, BC009033.1, AK026592.1, AF177336.1, BC008485.1, AB047801.1, AF207829.1, AK025772.1, BC008899.1, AL080137.1, BC006807.1, AL133077.1, AK026532.1, AK000618.1, AK027113.1, AK026959.1, AB052191.1, AL133093.1, AB047887.1, Z82022.1, AK026947.1, AK027193.1, AF162270.1, AB063084.1, BC009341.1, AL137476.1, AK026533.1, AK027114.1, AB051158.1, AF146568.1, AB050510.1, AK026045.1, BC008280.1, BC003682.1, AL080127.1, AL133075.1, Y14314.1, AL117440.1, AL136845.1, AK026551.1, AK000718.1, AL122110.1, AL122049.1, AK026480.1, AL133080.1, AL049382.1, AL133640.1, AB048919.1, AL117583.1, AL133098.1, AK026784.1, AL117585.1, AL162062.1, AL136864.1, AL133113.1, AL133072.1, AL122123.1, X72889.1,

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3	HWMMO59	31	1356977	
4	HSSJJ51	5	900561	BF526701, BF873331, BF929164, BF221973, AV688712, BF743216, AI682301, BF929165, AA368885, BE295879, AI078870, BE270667, AI611295, BF963547, AA323287, BF763407, BF002002, BF002176.
5	HCEWD38	6	1284936	AA746177, AI510718, R37382, AI247745, R52665, AA323018, H49570, N55573, BG236027, AW966998, AA323159, AL039810, R13472, AL039789, BF332816, AW955388, BF879416, AA304816, AW964665, AA323409, R52713.
5	HCEWD38	32	616396	AA323018, AA323159, AW966998, R13472, AW955388, AA304816, AW964665, AA323409,

				R52713, AL132800. 4.
5	HCEWD38	33	411082	R37382, AA746177, AI510718, R52665, AI247745, AA323018, N55573, BG236027, H49570, AW966998, AA323159, R13472, AW955388, AL039810, AA304816, BF879416, AW964665, AA323409, AL039789, BF332816, R52713.
6	HUCMC56	7	1310874	R20045, AW965432, AA332557, R36770, R60458, AA340432, AW163243, AX018985, AX018987, M58583, S76975, AL117383.
6	HUCMC56	34	967258	R60458, AW163243.
7	HWLZU06	8	1310875	BF055285, BF882978, AW070344, AI805087, BF906443, AI083823, W92687, AI085548, AI083824, W92830, BE138819, AW192716, AW150070, BF588518, AA775561, BF764330, AW172659, M91217, AI393090, AW137263, F33371, W05570, R70460, AA339837, AI564511, AA359338, AW380993, AW960500, AW192211, AI924106, AA377546, AI346326, AI825277, BF724241, AI432310, AI144286, AA301724, AI619600, AI783751, AI470161, AI457948, AW190639, AI338249, AW025095, AL110261, AF086482.
7	HWLZU06	35	933581	BF055285, BF882978, AI346326, AI432310, AI144286, AI805087, AW070344, AI338249, BF906443, AI457948, AI083823, AI470161, AI085548, W92687, AI083824, W92830, BE138819, AW192716, AW150070, BF588518, AA775561, BF764330, AW172659, AI393090, M91217, F33371, W05570, AW137263, R70460, AA339837, AI928593, AI564511, AA359338, AW380993, AW960500, AI924106, AA377546, AW192211, AI825277, AA301724, AI619600, AI783751, BF724241, AA704632, AW190639, N76120, AW025095.
8	HDPBA69	9	905708	BF343049, BF525949, AI300176, BF342466, AI193100, AW953836, N32601, AA894528, BF526118, AI749282, AA917673, AI200645, AA577400, AW001112, AI342526, AI561024, AA922077, BF339231, BG060138, AI274361, AW629891, AI811138, AI682589, AI598054, BF821354, AA703086, BF821349, AW000838, AI687717, BF879161, AI346224, AI283829, AW966426, BF878968, AI718510, N38801, AA609464, AA443822, AI285277, AI141075, C17007, AA827271, AI274203, AI278912, AW953891, AA485613, AI291153, AI184968, AI815092, BF879241, AA922163, AA954441, W92736, AI523358, AI582743, AI272748, T95291, AI304507, AW858976, BF823040, R47871, H90673, R71353, AV689909, W92820, AW515183, AA640081, R47872, AI749077, AA508675, AA025765, AI352318, H66699, R66274, T27046, H78056, AI873364, H66689, AW029317, AI336608, H64116, AI872250, H42114, T95371, AA383872, R24350, AI749260, BF087543, T72087, AA025953, BF820542,

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8	HDPBA69	36	906482	BF343049, BF525949, AI300176, BF342466, AW953836, AI749282, AA894528, N32601, BF526118, AI193100, AA577400, AI200645, AA917673, AW001112, AA703086, AI687717, AI342526, AI561024, BF339231, AI141075, AA922077, AW629891, AI274361, AI184968, AA922163, AI815092, BF821349, W92736, BF821354, AI682589, AW000838, BF879161, BF878968, AI346224, AI718510, AI283829, N38801, AW966426, AA443822, AA609464, C17007, AI285277, BG060138, AA827271, AW953891, AI274203, AA485613, AI811138, AI278912, BF879241, AI291153, AI598054, AA954441, AW515183, AI272748, AI304507, T95291, AA508675, AW858976, AI582743, BF823040, R47871, R71353, AV689909, W92820, AA640081, R47872, AI749077, AI523358, AA025765, AI459266, H64116, T27046,

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8	HDPBA69	37	906481	AI346224, AI291153, AA922163, AI352318, AI342526, W92736, AA577400, AW000838, AA508675, AI598054, AI815092, AI749077, AI523358, AA703086, N38801, AI718510, AW001112, AA025765, AI561024, H66689, AW515183, H66699, R47872, AI873364, AI184968, AA894528, N32601, AI274361, AI274203, AI459266, AI200645, AI687717, AI682589, AI285277, AA917673, BG060138, AI193100, AA922077, AI283829, AI749260, AI272748, AA827271, AI141075, AA443822, AI300176, AI749282, AA609464, AI278912, AI088641, T95291, AI582743, H90673, AA954441, H78057, AI304507, AI811138,

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8	HDPBA69	38	906480	BF343049, BF525949, BF339231, AW629891, R47871, T27046, H42114, H64116, BF342466, H64951, N90491, H01871, H01130, H89819, N45434, H26462, H27838, BF526118, T72232, H83150, BF991147, AA640081, N47826, BE769806, AV689909, BF737942, R17629.
9	HLWAE11	10	783071	AI344312, AI276017, AI476822, AI139478, AI160906, AI240398, AW001088, AA425919, AA011278, AA428788, AI354692, AI089176, AA622689, BF431807, AI968918, N68826, AI467807, BF436247, AW673768, AW135943, R24434, R16812, R31419, R31434, R24435, H83155, AI865939, R31418, AW673133, W67349, R31433, AA027080, R28030, BE542160, T81223, AI631986, AA677315, BF760063, AI872675, BF331923, BE926682, BE926741, AF329842.1, Z82188. 2.
10	HSZAF47	11	1283068	AW298370, AI433823, AI239867, D62170, D61860.
10	HSZAF47	39	456551	AW298370, AI433823, AI239867, D62170, D61860, AF329839.1, AC007016. 5.
11	HWTAY65	12	908762	AI916779, AW304481, AA732948, AI288625, AW965223, AA443244, AA194106, W79527, BF511014, AI038644, AA443206, W93527, AA346195, W79559, BE296248, BE269743, AF329836. 1.
11	HWTAY65	40	905611	AI916779, AW304481, AA732948, AI288625, AW965223, AA443244, AA194106, W79527, BF511014, AI038644, AA443206, W93527, AA346195, W79559, BE296248, AW975618, AW960414, AV724520, D51799, C14389, C14331, AW960553, AW966531, AW964468, AV718692, AW956397, AV720791, AV718489, AW973541, AW965175, AW949645, AW978634, AW966013, AW973307, AV720533, AW973474, D81030, AW949642, AW966059, AV720211, C14429, AW959202, AW966053, D80212, AW964756, AW960465, AW959136, D80166, AV718707, AV719822, AV719557, AW959799, AV720731, D59859, AW964477, AW966022, AW966029, AV718938, D80188, AV718633, AW975613, D51423, D59619, AW965177, AW949630, AW978661, D80210, AW966075, AW973488, D80240, D80253, AW966065, AV719324, AW949629, AW975605, AW973334, AV718931, AV720878, AW966032, AW966534, AV699447, D58283, AW958993, AV722801, AV723927, AW949656, AW966041, AW949631, AW949643, AW949618, AW949657, D59275, AW973482,

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12	HHGDP51	13	1310873	AI652297, BF967925, AW769372, BE857943, AA446941, BF115527, AI209086, AA443365, BF059139, D59611, AW204677, AI446405, AI918554, BE538466, BE965527, AW079768, BF816041, BF816031, AW082600, AW893295, BF885675, BF915537, AI537837, AA464646, AI582912, BF987113, AA835966, AI865116, AI620093, AI573026, AW058233, AV735118, AI889147, AI371228, AI349957, AA848053, AI345005, AI627880, AW084132, AW020592, BE613727, BG057418, AI345014, AW022494, N22406, AW020288, AI560679, BF913615, AW059713, AI636719, BE966928, BF817746, BF925348, BF915316, AI349814, BE875407, AW858254, AI583578, AW083804, AA830821, BG105895, AW075084, AI310925, BE904051, AI312399, AI349937, AI623736, AI334884, AI307543, AW411043, AI345251, BE245461,

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				AF217991, AB049848, X99257, AK026651, AB049629, AF114818, AL133098, AJ242859, AL117585, AL080127, U00686, AF040751, AL137705, A12297, A93016, I00734, AK026395, AL162083, AF119894, AK024594, AK000445, L40363, AB047897, AL133081, AK000212, AK025669, AK025573, AF188698, AB049758, E00617, E00717, E00778, AX027129, AF261883, A18788, AJ006417, U75370, U57352, AK025889, E02914, AL137283, AL133645, X70685, U57715, AK026541, I17767, AB046642, AB044390, AK000291, AL110225, AL389951, S53987, AL117394, AF119358, AF057300, AF057299, AF242525, I89944, AK026592, AK027105, AF117959, I09360, AK026571, AR038969, E15582, AK026924, AF111847, AL137547, X59414, AL110222, AK024538, AK026608, D55641, Z22828, AK026591, AF078844, AL080060, Y16258, Y16257, E02756, Y16256, AF065135, AF130054, Z72491, AF203473, AL353957, AF119909, AK025208, AL137648, U66274, AR079011, AR079012, A90832, AL137555, AL137659, AL117629, U77594, AK025383, AF030165, AF012536, AF003737, AK026533, AF116676, AB047248, AL389978, AF159141, AK027104, AF067420, U90884, AL359600, AF116644, AF031147, I26207, AL157479, AF017790, AK025541, AL117578, AK026452, X54971, AX011676, AL080137, AF000145, U72620, AB047904, AC004227, AK026600, A08916, AK026629, S75997, AF113694, AR068751, AF110329, AL133067, AL049464, S63521, AF022813, AL137557, AL133558, AX046603, AK026353, AF051325, AB047966, AX005848, AX005804, AX014095, AK025084, I46765, AL137459, AB026675, AK025491, AK025349, AF311287, AB038698, U68233, I92592, E07108, AR059883, AF130068, AF036268, AF260566, AK000391, AF016271, AF178432, AL389939, AF040723, AB029065, AF114168, AC010128, AC005902, AL137276, AL110171, AF314091, Y10655, AF116691, X76228, AL133054, AF090943, AF218031, AK025391, AK027129, AF218004, AB047615, AK025906, AF069506, AK026164, AL359596, M30514, AL050280, I52013.
12	HHGDP51	41	857703	AI652297, BF967925, AW769372, BE857943, BF115527, AA446941, AI209086, AA443365, D59611, BF059139, AW204677.
13	HBCBS41, HDMBJ47	14	1310706	BF525534, BF525878, AI188462, AV706177, AA835791, AI573089, AV706657, AA828067, BF338495, AI141312, AI961924, AA563724, AI829025, AV733099, AA464950, AA845819, AA618072, AI343736, AA576567, AI370917, AA622849, AI591077, AA039329, AW084144, AI719443, AA978073, BE819803, AI968544, AA910242, AI344535, AI554230, BF994888,

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13	HBCBS41, HDMBJ47	42	1225229	BF525534, BF525878, AI188462, AV706177, AI573089, AA835791, AV706657, AA828067, BF338495, AI141312, AI961924, AA563724, AI829025, AV733099, AA576567, AA464950, AA845819, AA618072, AI343736, AI370917, AA622849, AW084144, AA039329, AI591077, AI719443, AA978073, BE819803, AI968544, AA910242, AI344535, AI554230, BF994888, AI299970, AI298788, AA948689, AA828804, BE219403, AV702739, AA775331, AA937438, N49449, AI299637, AA516376, T70926, H27042, AI565682, AA933874, AV706862, AA953314, AW951361, AA838059, AA865068, AI097249, AA663921, AA338264, R68898, AV707811, AV703148, AI879461, AA394279, AA582298, BE138913, AA879122, AW238763, H26166, AA039414, AW383740, BF951235, AW951363, AI125081, AA577157, AA582289, BF591527, AI299684, AA603650, AA465026, AA837695, AW137828, N54606, T95006, AA828747, BF945969, AI720693, AA834499, H26167, T91949, N33604, BG236868, AW087254, AA295894, AA293797, R68796, AA988656, AI817977, T49380, AA628820, AA379748, AW628890, AI589170, AW516492, AI079151,

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13	HBCBS41, HDMBJ47	43	933547	AI188462, AA835791, AV706657, BF338495, AI141312, AA563724, AA828067, AI573089, AI829025, AI961924, AA576567, AV733099, AA464950, AA622849, AW084144, AI370917, AA845819, AA618072, AI343736, AA039329, AI591077, AA910242, AI719443, AA978073, AI968544, AI344535, AI298788, AI554230, AV702739, AI299970, AA948689, BF994888, T70926, AI299637, AA516376, BF525534, BE219403, AA775331, AA937438, N49449, H27042, AI565682, AI097249, AA838059, AA933874, AA865068, AV706862, AA953314, AA663921, BF945969, BE819803, AV706177, R68898, AA879122, BF525878, AA582298, AV707811, AI879461, AV703148, AA603650, AA394279, AA039414, BE138913, AW383740, H26166, AW238763, AA582289, BF951235, AA577157, BF591527, AI299684, AW951361, AI125081, N54606, T95006, N33604, AI720693, AW137828, AA834499, H26167, BG236868, AA465026, T91949, AA828804, AA295894, AW087254, R68796, AA293797, AW951363, AI817977, T49380, AA988656, AA628820, AW628890, AW516492, BF842441, AI079151, AW815770, AI582116, AI589170, AA984912, R36633, AI000183, AI581583, AA837695, T71284, T53830, AI950559, AA369370, BG059309, T94953, AI869893, BE465572, AI826458, T86179, T86178, AI749183, T53963, AA369395, AI344355, BG153207, AA486985, R28940, AA913653, AW797707, AI582011, AI749099, AW798220, AA369514, BF951201, AA603651, AA379748, AI676040, T71421, T28386, N76686, R39712, AI734970, AA362998, AL047857, AA913190, AA369611, BF379002, AA318607, T70988, AW816674, AA369396, T72203, AI719214, BF870900.
13	HBCBS41, HDMBJ47	44	967511	BF525534, BF525878, AV706657, AI188462, AV706177, AW084144, AA618072, AI573089, AA835791, BF338495, AA828067, AI141312, AI961924, AA563724, AI829025, AV733099, AA576567, AA464950, AA845819, AI343736, AI370917, AA838059, AA622849, AA039329,

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14	HDPRZ06	15	1384228	BE622709, BE622543, AW195694, AA449506, BE349118, AW836407, BE218589, BE018663, AI671569, AI990535, AI338971, AI656295, BF352595, BF352547, BF353066, AA449077, BF902513, BF756315, AA991669, AA971051, AA009692, AA837005, AA009411, AA639511, AA365182, AA365181, AW236877, AI766763, BF214429, AW983562, AV704180, BF195732, AV703542, BF352031, AA045125, AV706910, BF368967, T03588, BE142783, AV704660, AV706223, AV727314, AV701643, AV660516, AV727978, AV726502, AV703591, AV731070, AV703266, AV660258, AV705550, AV727238, AV728436, AV706851, AV652001, AV705518, AV725577, AV727954, AV729424, AV727139, AV702322, AV725618, AV705992, AV726337, AV653353, AV704626, AW959346, AV727822, AV728743, AV702149, AV652528, AV728404, AV651897, AV725441, AV725031, AV707024, AV708786, AV725582, AV709580, AV708872, AV726194, AV704144, AV726392, AV727618, AV727583, AW955629, AV725991, AV729255, AV703168, AV726590, AV725255, AV703632,

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14	HDPRZ06	45	1303540	BE622709, BE622543, AW195694, BE349118, AA449506, BE218589, AI671569, AI990535, AI656295, AA449077, BF902513, BE018663, AA971051, AA991669, AA009411, AA009692, AA837005, AA639511, AA365182, AA365181, AW236877, AI766763, BF214429, BE142783, AW971745, AA887644, AL134524, AW968355, AW877209, AW972092, AL119324, AW968356,

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14	HDPRZ06	46	1223606	
15	HKB1F69	16	1286614	AI417523, BG120479, AI749321, AW057748, AW043700, AW057920, AW305168, AA608713, AW474850, AA404349, BF594226, BF541540, AW022120, AA579971, AA629969, AI127940, AU151624, AW005378, AA705289, AW377397, AI610162, AA625142, AI689091, AA887126, AA835810, AA181946, AI084438, AW450806, BE378048, BF149104, AA133172, AI269303, AI378772, AA470804, R56253, AA707300, AA725191, R99908, W42777, AI540847, AA766559, AA496910, T78435, AA256605, AA683171, AI536732, AW021074, BF589574, BF062307, AI359641, AA694404, AA903168, AA258076, AI537144, AI264091, AW191603, R42797, BF727469, N95366, AA354837, AA083067, AA134604, AW301165, Z41690, R48102, H48756, N66512, R40560, AI270253, C01933, AW473992, AA497072, R44523, R47988, T97892, AA362636, R49171, T23045, F04485, R55714, AW889340, BE155973, AA775162, AW902313, BE243585, T75572, AI967943, AL119457, AL042544, AL119399, AL119511, AW877209, AL119324, T97891, AA258647, AL042382, AL043152, AL079794, BG032704, AW970048, AL043168, AL037081, T61538, AL042866, BG113493, AW971745, BG164558, AL037104, AI554245, AI538028, BG168640, AL134524, BF525578, AI133559, BE536058, BG260144, BG029053, BE968711, BF970449, AW827289, AW827276, AV756359, BE047852, BF338723, BE785868, AI784219, BE876033, AI364788, BF038131, BG256592, BE880182, BF806065, BG034459, BF822127, BE874133,

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16	HOHBO69	17	1282370	BG114252, BF344333, AW029321, BE619018, BF591735, AI084509, BE877796, AW068693, BF002157, AW068694, AA872420, N23787, AW613589, AI752218, AW630180, AI752219, AI752163, AI750192, AI753307, AI752164, N24399, AA789067, BF197886, W19235, AI424724, AA233788, AW392772, AW068274, AA627580, AA853772, AA853676, H99150, H89055, AA853685, BF448509, BF741968, BF132395, AA577443, AW392783, H99383, D79968, D62487, AA853675, AA290849, AA283763, W25429, AA853686, X57527, J05042, X66977, AF044969, AF054891, S63458, X66976, AF055330, AC007275, AF170702, AL022143.
16	HOHBO69	47	1280342	None
17	HCEES60	18	1305240	BG251391, AL138070, AA639738, AL138071, R38469, AA317570, W30872, AA043621, AA853712, AI806793, AA702490, AA780815, AI751694, AL138787, M60832, M60833.
18	HDALV07	19	1316192	AR034253, D45371, AB012165, AJ131461, AR034252, U49915, AJ131460, AB012164.
19	HEQAH47	20	877634	AL519977, BE383449, AL043766, BF061686, BF221776, BF310701, BF060773, BF434074, BF062728, AI659849, BE313561, BF314046,

				BF316323, AI659290, AI824840, BF061701, BF312471, AI751263, AI685765, AI591068, AI587181, AI920932, AI400351, AI148305, AI955664, AI652541, AI675888, AI653379, AI424943, AI128448, BE313794, BF437698, AI275016, BF590996, AI561014, AI660936, AI491938, AI968617, BE047763, AI127265, AA643524, BF313828, AI866540, AI751264, AI828892, AI824814, AA970985, BE855979, AI589275, AI768084, AA477627, AW371357, AI926713, AI969893, AI335684, AA057195, AA478085, AW193325, AW002099, AI672890, AI991492, AI225080, AW191017, AI804237, AI918988, AI215462, AI660046, AW263221, AW166456, AW361968, AI923034, BF939318, AI672957, AW008276, AI421034, BF941981, AA101823, AI474549, BF514389, AA968480, AW591386, AI972480, AI758252, AI277535, AI611291, AI446797, AA627406, AW082500, AI673160, AA127893, AW085658, AA101824, AI491939, AI445814, AW513225, AI656563, W21432, AW590943, AA128143, AW196052, AW452957, AI419247, AI356191, BF593921, AI339204, AA973738, BF196865, AA973140, BF941530, AA423796, AA962026, AI572714, BF593478, AA057129, AA834119, AI333104, AI401697, AI539260, AI628325, AI345415, AW163834, AI590043, AI698391, AI440238, AL047763, AW130362, AI523973, AW150622, AW008166, BF531023, AA565269, AL042567, AI361701, AI619820, AI434731, AI653402, AI880111, AI500061, AI345688, AI862067, AI800648, BE393784, AL037602, AI872423, AI524179, AI289791, AI927233, AI565172, AL037582, AI866469, AI370623, AL079963, AI678446, BG250475, AW189716, BF909758, AW196720, AW129659, AW081383, AI784214, BE964705, AV659072, AI244343, AI445611, AI680467, AI250646, BG260772, BE877401, BE907624, BG034598, AI699823, BF724420, BE904851, BF750886, AI869125, AI869377, AI582932, BE957870, AI638644, AA659688, AL036241, AI972112, AI345612, BE867194, BF035213, BE905161, BE873695, BE877904, AI345416, BE967004, AI627714, AW188525, AI251221, AL036673, BG169738, BF525838, AI290677, BG256090, AI470717, AI499570, BE963809, AW051088, AW983832, AW117882, AI471282, AI621341, AI440239, AW130104, AI866127, W45039, AI536574, AI583558, AI583578, BG118199, AI889189, AW075382, AI348847, AW083572, AW161202, AI366959, AI633125, AI800341, AI310575, AI869765, AI860027, AI538564, AI335476, AI866040, AI915291, AW152182, AI538817, AW130534, AI274655, AW025279, AI284060, BE965159, AI866770, BF811804, AI581362, AI270295,

				BE891834, BF669151, AV681858, AW073824, AI589428, AL050138.1, AF088916.1, BC007530.1, AF162780.1, Y09340.1, AL137480.1, BC000090.1, AK026542.1, AL080146.1, BC007522.1, BC001675.1, BC002491.1, AL162002.1, AB060889.1, BC006091.1, AJ012582.1, AL137558.1, AL389935.1, BC001199.1, AK026462.1, AL161802.15, AL117587.1, BC001166.1, AF183393.1, BC007571.1, BC003104.1, BC002631.1, AB055303.1, AB060887.1, BC007767.1, AL136765.1, BC006345.1, AK000618.1, BC008708.1, BC006119.1, Y14040.1, BC008364.1, BC001785.1, BC004925.1, AF249267.3, AL080154.1, AK027161.1, AL080110.1, AL117438.1, BC003410.1, BC003569.1, BC008382.1, AK024974.1, AK027160.1, AL136864.1, BC003101.1, AK000655.1, AL049382.1, AB047627.1, AL137292.1, BC008591.1, AL137530.1, AK027102.1, AK025435.1, AF044323.1, BC001964.1, U73682.1, AB060876.1, BC002911.1, BC003587.1, BC002370.1, AL442083.1, AF132730.1, BC000570.1, AL136752.1, AL136893.1, AL137495.1, AK026633.1, AL359583.1, BC002535.1, AL117416.1, BC006410.1, AL512718.1, AL137574.1, BC003590.1, AL133088.1, X66417.1, AL137461.1, U70981.1, AK024533.1, BC003573.1, AB050410.1, BC003591.1, AK025099.1, Z82022.1, AF271781.1, BC002471.1, AB050431.1, BC005854.1, AK025113.1, AL137256.1, AF369701.1, AL080148.1, AL133049.1, X53587.1, AF026816.2, AL359941.1, BC004945.1, BC004292.1, AK000418.1, AL136850.1, AL080159.1, AB060897.1, AF339775.1, BC004908.1, BC009333.1, AL137533.1, AF195092.1, BC007381.1, BC008649.1, AK027095.1, S76508.1, BC005002.1, X83544.1, BC004119.1, Y14314.1, BC000235.1, AL389982.1, BC006181.1, AL136784.1, BC001082.1, BC000751.1, AK024588.1, AK025860.1, AK025084.1, AB063074.1, S77771.1, U37359.1, BC002473.1, AL136774.1, BC005070.1, BC000860.1, AL133559.1, S61953.1, AK000476.1, BC000199.1, AB060864.1, AF245044.1, AL137478.1, BC008686.1, BC006103.1, BC005816.1, BC007460.1, AK025798.1, BC002466.1, AF124728.1, AF104032.1, AL137550.1, AF106862.1, X82434.1, L19437.2, AL137557.1, AL162003.1, BC004899.1, AK026164.1, AL137271.1, AB060837.1, AF141289.1, AB060916.1, BC004395.1, AK025350.1, AL137554.1, BC002356.1, AL353956.1, BC001844.1, AL080126.1,

				AL050092.1, BC008078.1, BC008417.1, AF271350.1, AL512751.1, BC007453.1, BC009026.1, AF131773.1, AL136615.1, BC000253.1, AK026647.1, AK026744.1, AL136844.1, AB056420.1, BC008717.1, BC008723.1, AL133062.1, BC006161.1, AF081571.1, AL050155.1, AF230496.1, AC026464.6, AF242525.1, BC002516.1, AF239683.1, BC004349.1, AL512684.1, AL133081.1, AF131821.1, AB047953.1, BC001763.1, AB048974.1, AJ299431.1, AL050149.1, BC005843.1, AF184965.1, AL136586.1, AL137488.1, AK024747.1, AL136768.1, AL122121.1, AL110280.1, AC006288.1, AK026506.1, BC004960.1, AL136884. 1.
19	HEQAH47	48	1254417	
20	HATNA88	21	1282006	BG032839, AI217963, AW665995, BG178505, AI032401, AI016792, AW973741, AA889643, BE041602, AW983637, AW983608, AW983601, AW983610, AW983628, AW983645, AW983688, AW983603, AW983607, AW983625, AW983640, AW983612, AW983642, AW983617, AW983624, AW983634, AW983687, AW983602, AW983630, AW983635, AW983636, AW983689, AW983616, AW983639, AW983609, AW983644, AW983618, AW983604, AW983611, AW983615, AW983619, AW983686, AW983622, AW983633, AW983605, AW983626, AW983631, AW983643, AW983627, AW983620, AW983638, AW983632, AW983613, AW983685, AW983621, AW983592, AA559283, AW983641, AW983623, AW983589, AW983593, BF349085, AW983594, AW983614, AA583866, AA883836, AA557662, AA593227, BF512098, AI275909, AA578056, AL445985, AX047347, AF178931.
20	HATNA88	49	1285117	

TABLE 3

cDNA Plasmid: V	Library Code(s)
HCE1P80	H0052 H0179 H0253 H0266 H0375 H0543 H0551 H0575 H0618 H0790 L1290 S0027
HUFGH53	H0009 H0012 H0024 H0059 H0087 H0208 H0483 H0506 H0529 H0540 H0617 H0622 H0624 H0625 H0660 H0672 H0687 L1290 S0038 S0354 S0374 S0418 S0444 S6026
HWMMO59	H0024 H0392 H0617 L1290 S0358 S0444
HSSJJ51	H0030 H0052 H0087 H0100 H0251 H0253 H0286 H0318 H0445 H0486 H0550 H0594 H0599 H0618 H0619 H0693 H0713 H0757 H0762 L1290 S0037 S0196 S0280 S0378 S0436 S0476
HCEWD38	H0052 H0194 H0261 H0581 L1290
HUCMC56	H0013 H0144 H0178 H0244 H0563 H0570 H0624 L1290 S0051 S0442
HWLZU06	H0549 S0222 S0406 S0436
HDPBA69	H0009 H0014 H0031 H0039 H0062 H0063 H0090 H0108 H0122 H0123 H0163 H0189 H0213 H0252 H0264 H0309 H0333 H0343 H0345 H0352 H0375 H0376 H0427 H0444 H0445 H0486 H0506 H0509 H0510 H0521 H0522 H0553 H0555 H0570 H0575 H0581 H0583 H0595 H0597 H0619 H0620 H0622 H0638 H0644 H0652 H0658 H0661 H0662 H0663 H0666 H0668 H0672 H0682 H0710 H0713 H0726 H0753 H0754 H0757 H0762 H0773 H0774 H0777 L1290 S0106 S0190 S0212 S0280 S0282 S0330 S0354 S0358 S0360 S0362 S0374 S0376 S0378 S0384 S0406 S0408 S0434 S0436 S0438 S0440 S0442
HLWAE11	H0050 H0056 H0266 H0521 H0553 L1290
HSZAF47	H0013 H0321 L1290
HWTAY65	H0012 H0013 H0019 H0123 H0351 H0352 H0550 H0553 H0570 L1290 S0007
HHGDP51	H0424 H0455 H0617 L1290
HBCBS41	H0004 H0009 H0014 H0031 H0042 H0068 H0086 H0087 H0090 H0124 H0144 H0190 H0255 H0263 H0309 H0327 H0329 H0351 H0370 H0375 H0376 H0393 H0415 H0421 H0427 H0441 H0445 H0486 H0489 H0521 H0522 H0538 H0549 H0550 H0553 H0555 H0575 H0581 H0583 H0587 H0591 H0592 H0606 H0617 H0638 H0641 H0644 H0646 H0649 H0653 H0658 H0659 H0662 H0672 H0673 H0689 H0690 H0710 H0716 H0722 H0726 H0753 H0754 H0755 H0762 H0768 H0777 H0778 H0789 L1290 S0010 S0031 S0036 S0044 S0260 S0280 S0328 S0354 S0356 S0358 S0360 S0374 S0376 S0406 S0408 S0434 S0436 S0440 S0442 S0444 T0068
HDPRZ06	H0124 H0188 H0250 H0271 H0328 H0486 H0521 H0522 H0539 H0540 H0580 H0638 H0641 H0645 L1290 S0044 S0116 S0344 S0426 S0434 T0006
HKB1F69	H0013 H0384 H0412 H0616 H0659 H0688 L1290 S0007 S0026

	S0222 S0402 S0444
HOHBO69	H0024 H0050 H0100 H0266 H0486 H0519 H0538 H0544 H0545 H0550 H0551 H0575 H0593 H0615 H0619 H0622 H0623 H0653 H0665 H0667 H0770 H0771 L1290 S0015 S0022 S0028 S0032 S0040 S0126 S0134 S0180 S0196 S0208 S0212 S0250 S0276 S0298 S0360 S0390 S0418 S0420 S0434 S3014
HCEES60	H0052 H0123 H0135 H0144 H0251 H0594 H0615 H0622 H0628 H0645 L1290 S0040 S0126 S0142 S0344 S0420 S0430 T0082
HDALV07	H0081 H0427 H0706 H0713 H0716 H0717 H0725 L1290 S0212 S0260 S0280 S6022
HEQAH47	H0544
HATNA88	H0599 H0616 H0708 H0713 L1290 S0216

TABLE 4

SEQ ID NO: X	Cytologic Band or Chromosome:	OMIM Reference(s):
2	22q13.2	188826 602049
4	17q25.2	603967 606800
5	14q11.2	162080 182600 186880 190195 600243 602279 603593 605463 606439 606675
7	11q23.3	176000 236680 261640 600644 602574 603113 604763 605201 607086
9	22q13.1	103050 124030 138981 182380 188826 190040 218040 602049 603590
12	11q11	606860
13	1p36.3-p34.1	115665 116600 120550 120570 120575 121800 130500 138140 142461 153390 153454 155600 164780 167410 171760 172411 172430 178300 185470 211420 256700 600423 600975 601990 602023 603324 603490 603688 603776 604630 604933 605225 605425 605747 605909 605995 606210 606324 606693 606811 606928 606953 606996 607093 607215
17	7p15-p12	107776 138079 139191 142958 142959 153880 165240 180104 203740 261670 600994 601472 601583 603023 603284 606224 606246
18	3q27	109565 120520 142640 210200 228960 600044 602322 603273 603285 603945 603959 605229 605441 605552 607037

TABLE 5

Library Code	Library Description	Disease
H0004	Human Adult Spleen	
H0009	Human Fetal Brain	
H0012	Human Fetal Kidney	
H0013	Human 8 Week Whole Embryo	
H0014	Human Gall Bladder	
H0019	Human Fetal Heart	
H0024	Human Fetal Lung III	
H0030	Human Placenta	
H0031	Human Placenta	
H0039	Human Pancreas Tumor	disease
H0042	Human Adult Pulmonary	
H0050	Human Fetal Heart	
H0052	Human Cerebellum	
H0056	Human Umbilical Vein, Endo. remake	
H0059	Human Uterine Cancer	disease
H0062	Human Thymus	
H0063	Human Thymus	
H0068	Human Skin Tumor	disease
H0081	Human Fetal Epithelium (Skin)	
H0086	Human epithelioid sarcoma	disease
H0087	Human Thymus	
H0090	Human T-Cell Lymphoma	disease
H0100	Human Whole Six Week Old Embryo	
H0108	Human Adult Lymph Node, subtracted	
H0122	Human Adult Skeletal Muscle	
H0123	Human Fetal Dura Mater	
H0124	Human Rhabdomyosarcoma	disease
H0135	Human Synovial Sarcoma	
H0144	Nine Week Old Early Stage Human	
H0163	Human Synovium	
H0178	Human Fetal Brain	
H0179	Human Neutrophil	
H0188	Human Normal Breast	
H0189	Human Resting Macrophage	
H0190	Human Activated Macrophage (LPS)	
H0194	Human Cerebellum, subtracted	
H0208	Early Stage Human Lung, subtracted	
H0213	Human Pituitary, subtracted	
H0244	Human 8 Week Whole Embryo, subtracted	
H0250	Human Activated Monocytes	
H0251	Human Chondrosarcoma	disease
H0252	Human Osteosarcoma	disease

H0253	Human adult testis, large inserts	
H0255	breast lymph node CDNA library	
H0261	H. cerebellum, Enzyme subtracted	
H0263	human colon cancer	disease
H0264	human tonsils	
H0266	Human Microvascular Endothelial Cells, fract. A	
H0271	Human Neutrophil, Activated	
H0286	Human OB MG63 treated (10 nM E2) fraction I	
H0309	Human Chronic Synovitis	disease
H0318	HUMAN B CELL LYMPHOMA	disease
H0321	HUMAN SCHWANOMA	disease
H0327	human corpus colosum	
H0328	human ovarian cancer	disease
H0329	Dermatofibrosarcoma Protuberance	disease
H0333	Hemangiopericytoma	disease
H0343	stomach cancer (human)	disease
H0345	SKIN	
H0351	Glioblastoma	disease
H0352	wilm's tumor	disease
H0370	H. Lymph node breast Cancer	disease
H0375	Human Lung	
H0376	Human Spleen	
H0384	Brain, Kozak	
H0392	H. Meningioma, M1	
H0393	Fetal Liver, subtraction II	
H0412	Human umbilical vein endothelial cells, IL-4 induced	
H0415	H. Ovarian Tumor, II, OV5232	disease
H0421	Human Bone Marrow, re-excision	
H0424	Human Pituitary, subt IX	
H0427	Human Adipose	
H0441	H. Kidney Cortex, subtracted	
H0444	Spleen metastic melanoma	disease
H0445	Spleen, Chronic lymphocytic leukemia	disease
H0455	H. Striatum Depression, subt	
H0483	Breast Cancer cell line, MDA 36	
H0486	Hodgkin's Lymphoma II	disease
H0489	Crohn's Disease	disease
H0506	Ulcerative Colitis	
H0509	Liver, Hepatoma	disease
H0510	Human Liver, normal	
H0519	NTERA2, control	
H0521	Primary Dendritic Cells, lib 1	
H0522	Primary Dendritic cells,frac 2	
H0529	Myoloid Progenitor Cell Line	
H0538	Merkel Cells	

H0539	Pancreas Islet Cell Tumor	disease
H0540	Skin, burned	
H0543	T cell helper II	
H0544	Human endometrial stromal cells	
H0545	Human endometrial stromal cells-treated with progesterone	
H0549	H. Epididiymus, caput & corpus	
H0550	H. Epididiymus, cauda	
H0551	Human Thymus Stromal Cells	
H0553	Human Placenta	
H0555	Rejected Kidney, lib 4	disease
H0563	Human Fetal Brain, normalized 50021F	
H0570	Human Fetal Brain, normalized C500H	
H0575	Human Adult Pulmonary,re-excision	
H0580	Dendritic cells, pooled	
H0581	Human Bone Marrow, treated	
H0583	B Cell lymphoma	disease
H0587	Healing groin wound, 7.5 hours post incision	disease
H0591	Human T-cell lymphoma,re-excision	disease
H0592	Healing groin wound - zero hr post-incision (control)	disease
H0593	Olfactory epithelium,nasalcavity	
H0594	Human Lung Cancer,re-excision	disease
H0595	Stomach cancer (human),re-excision	disease
H0597	Human Colon, re-excision	
H0599	Human Adult Heart,re-excision	
H0606	Human Primary Breast Cancer,re-excision	disease
H0615	Human Ovarian Cancer Reexcision	disease
H0616	Human Testes, Reexcision	
H0617	Human Primary Breast Cancer Reexcision	disease
H0618	Human Adult Testes, Large Inserts, Reexcision	
H0619	Fetal Heart, reexcision	
H0620	Human Fetal Kidney, Reexcision	
H0622	Human Pancreas Tumor, Reexcision	disease
H0623	Human Umbilical Vein, Reexcision	
H0624	12 Week Early Stage Human II, Reexcision	
H0625	Ku 812F Basophils Line	
H0628	Human Pre-Differentiated Adipocytes	
H0638	CD40 activated monocyte dendridic cells	
H0641	LPS activated derived dendritic cells	
H0644	Human Placenta (re-excision)	
H0645	Fetal Heart, re-excision	
H0646	Lung, Cancer (4005313 A3): Invasive Poorly Differentiated Lung Adenocarcinoma,	
H0649	Lung, Normal: (4005313 B1)	
H0652	Lung, Normal: (4005313 B1)	

H0653	Stromal Cells	
H0658	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	disease
H0659	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	disease
H0660	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	disease
H0661	Breast, Cancer: (4004943 A5)	disease
H0662	Breast, Normal: (4005522B2)	
H0663	Breast, Cancer: (4005522 A2)	disease
H0665	Stromal cells 3.88	
H0666	Ovary, Cancer: (4004332 A2)	disease
H0667	Stromal cells(HBM3.18)	
H0668	stromal cell clone 2.5	
H0672	Ovary, Cancer: (4004576 A8)	
H0673	Human Prostate Cancer, Stage B2, re-excision	
H0682	Ovarian cancer, Serous Papillary Adenocarcinoma	
H0687	Human normal ovary(#9610G215)	
H0688	Human Ovarian Cancer(#9807G017)	
H0689	Ovarian Cancer	
H0690	Ovarian Cancer, # 9702G001	
H0693	Normal Prostate #ODQ3958EN	
H0706	Human Adult Skeletal Muscle	
H0708	Human Skeletal Muscle	
H0710	Acute Myeloid Leukemia /SGAH (Patient #6)	
H0713	Adipose tissue (diabetic type I, obese) #41706	
H0716	Adipose tissue (diabetic type II)#41689	
H0717	Adipose tissue (diabetic type II) #41661	
H0722	Diabetic Liver 99-09-A281a	
H0725	Normal Adipose Tissue #41838-08	
H0726	Normal skeletal muscle #96-08-A171	
H0753	pancreatic cancer sample # 4004959A1	
H0754	Pancreatic cancer #14677A1L	
H0755	Pancreatic cancer sample#4004959 A1	
H0757	normal pancreas #400556A8	
H0762	Normal Pancreas 42206	
H0768	Lung cancer	
H0770	Esophageal Cancer #2109A5A ductal carcinoma	
H0771	esophageal cancer #0011C075Ra	
H0773	Malignant Esophagus #9706C049	
H0774	Prostate infiltrated by adenocarcinoma #4007645B1	
H0777	esophageal cancer #9902C094	
H0778	Esophageal Cancer #9804C013Rb	
H0789	renal cell carcinoma of kidney	
H0790	HMC-1 untreated	

L1290	Soares_testis_NHT	
S0007	Early Stage Human Brain	
S0010	Human Amygdala	
S0015	Kidney medulla	
S0022	Human Osteoclastoma Stromal Cells - unamplified	
S0026	Stromal cell TF274	
S0027	Smooth muscle, serum treated	
S0028	Smooth muscle,control	
S0031	Spinal cord	
S0032	Smooth muscle-ILb induced	
S0036	Human Substantia Nigra	
S0037	Smooth muscle, IL1b induced	
S0038	Human Whole Brain #2 - Oligo dT > 1.5Kb	
S0040	Adipocytes	
S0044	Prostate BPH	disease
S0051	Human Hypothalmus,Schizophrenia	disease
S0106	STRIATUM DEPRESSION	disease
S0116	Bone marrow	
S0126	Osteoblasts	
S0134	Apoptotic T-cell	
S0142	Macrophage-oxLDL	
S0180	Bone Marrow Stroma, TNF&LPS ind	disease
S0190	Prostate BPH,Lib 2, subtracted	
S0196	Synovial IL-1/TNF stimulated	
S0208	Messangial cell, frac 1	
S0212	Bone Marrow Stromal Cell, untreated	
S0216	Neutrophils IL-1 and LPS induced	
S0222	H. Frontal cortex,epileptic,re-excision	disease
S0250	Human Osteoblasts II	disease
S0260	Spinal Cord, re-excision	
S0276	Synovial hypoxia-RSF subtracted	
S0280	Human Adipose Tissue, re-excision	
S0282	Brain Frontal Cortex, re-excision	
S0298	Bone marrow stroma,treated	
S0328	Palate carcinoma	disease
S0330	Palate normal	
S0344	Macrophage-oxLDL, re-excision	
S0354	Colon Normal II	
S0356	Colon Carcinoma	disease
S0358	Colon Normal III	
S0360	Colon Tumor II	disease
S0362	Human Gastrocnemius	
S0374	Normal colon	
S0376	Colon Tumor	disease
S0378	Pancreas normal PCA4 No	

S0384	Tongue carcinoma	disease
S0390	Smooth muscle, control, re-excision	
S0402	Adrenal Gland,normal	
S0406	Rectum tumour	
S0408	Colon, normal	
S0418	CHME Cell Line,treated 5 hrs	
S0420	CHME Cell Line,untreated	
S0426	Monocyte activated, re-excision	
S0430	Aryepiglottis Normal	
S0434	Stomach Normal	disease
S0436	Stomach Tumour	disease
S0438	Liver Normal Met5No	
S0440	Liver Tumour Met 5 Tu	
S0442	Colon Normal	
S0444	Colon Tumor	disease
S0476	Epithelial-TNFa and INF induced	
S3014	Smooth muscle, serum induced,re-exc	
S6022	H. Adipose Tissue	
S6026	Frontal Lobe, Dementia	
T0006	Human Pineal Gland	
T0068	Normal Ovary, Premenopausal	
T0082	Human Adult Retina	

TABLE 6

OMIM Reference	Description
103050	Adenylosuccinase deficiency Autism, succinylpurinemic
107776	Colton blood group, 110450 [Aquaporin-1 deficiency]
109565	Lymphoma, B-cell
115665	Cataract, congenital, Volkmann type
116600	Cataract, posterior polar
120520	Membranous glomerulonephritis, antenatal [Neutral endopeptidase deficiency]
120550	C1q deficiency, type A
120570	C1q deficiency, type B
120575	C1q deficiency, type C
121300	Coproporphyria Harderoporphyrinuria
121800	Corneal dystrophy, crystalline, Schnyder
124030	Debrisoquine sensitivity Parkinsonism, susceptibility to

126453	Dystonia, primary cervical Blepharospasm, primary benign, 606798
130500	Elliptocytosis-1
138079	Diabetes mellitus, neonatal-onset, 606176 Hyperinsulinism, familial, 602485 MODY, type II, 125851
138140	Glucose transport defect, blood-brain barrier, 606777
138981	Pulmonary alveolar proteinosis, 265120
139191	Growth hormone deficient dwarfism
142461	Dyssegmental dysplasia, Silverman-Handmaker type, 224410 Schwartz-Jampel syndrome, type 1, 255800
142640	Thrombophilia due to HRG deficiency Thrombophilia due to elevated HRG
142958	Radioulnar synostosis with amegakaryocytic thrombocytopenia, 605432
142959	Guttmacher syndrome, 176305 Hand-foot-uterus syndrome, 140000
146200	Hypoparathyroidism, familial
153390	SCID due to LCK deficiency
153454	Ehlers-Danlos syndrome, type VI, 225400
153880	Macular dystrophy, dominant cystoid
155600	Malignant melanoma, cutaneous
162080	Retinitis pigmentosa, autosomal dominant
164780	1p36 deletion syndrome
165240	Greig cephalopolysyndactyly syndrome, 175700 Pallister-Hall syndrome, 146510 Polydactyly, postaxial, types A1 and B, 174200 Polydactyly, preaxial, type IV, 174700
167410	Rhabdomyosarcoma, alveolar, 268220
171760	Hypophosphatasia, adult, 146300 Hypophosphatasia, childhood, 241510 Hypophosphatasia, infantile, 241500
172411	Colorectal cancer, resistance to
172430	Enolase deficiency
176000	Porphyria, acute intermittent Porphyria, acute intermittent, nonerythroid variant
178300	Ptosis, hereditary congenital, 1
180104	Retinitis pigmentosa-9
182380	Glucose/galactose malabsorption, 606824
182600	Spastic paraplegia-3A
185470	Pheochromocytoma, extraadrenal, and cervical paraganglioma, 115310
186880	Leukemia/lymphoma, T-cell
188826	Sorsby fundus dystrophy, 136900
190040	Dermatofibrosarcoma protuberans Giant-cell fibroblastoma

	Meningioma, SIS-related
190195	Ichthyosiform erythroderma, congenital, 242100 Ichthyosis, lamellar, autosomal recessive, 242300
190300	Tremor, familial essential, 1
203740	Alpha-ketoglutarate dehydrogenase deficiency
210200	3-Methylcrotonylglycinuria I
211420	Breast cancer, ductal
218040	Costello syndrome
228960	[Kininogen deficiency]
236680	Hydrolethalus syndrome
256700	Neuroblastoma
258900	Oroticaciduria
261630	Phenylketonuria due to dihydropteridine reductase deficiency
261640	Phenylketonuria due to PTS deficiency
261670	Myopathy due to phosphoglycerate mutase deficiency
600044	Thrombocythemia, essential, 187950
600243	Temperature-sensitive apoptosis
600423	Hirschsprung disease, cardiac defects, and autonomic dysfunction
600467	Malignant hyperthermia susceptibility 4
600532	Parkinson disease, susceptibility to, 168600
600593	Craniosynostosis, Adelaide type
600644	Cleft lip/palate ectodermal dysplasia syndrome, 225000 Ectodermal dysplasia, Margarita Island type, 225060 Zlotogora-Ogur syndrome, 225000
600882	Charcot-Marie-Tooth disease, type 2B
600975	Glaucoma 3, primary infantile, B
600994	Deafness, autosomal dominant 5
601472	Charcot-Marie-Tooth neuropathy, type 2D
601583	Wilms tumor susceptibility-5
601990	Neuroblastoma
602023	Bartter syndrome, 241200 Bartter syndrome, antenatal, 601678
602049	Neutrophil immunodeficiency syndrome
602279	Oculopharyngeal muscular dystorphy, 164300 Oculopharyngeal muscular dystrophy, autosomal recessive, 257950
602322	Dyskeratosis congenita, 127550
602574	Deafness, autosomal dominant 12, 601842 Deafness, autosomal dominant 8, 601543 Deafness, autosomal recessive 21, 603629
602630	Holoprosencephaly-4, 142946
602773	Renal cell carcinoma 4
603023	Leukemia, acute lymphoblastic
603113	Lung cancer, 211980
603273	ADULT syndrome, 103285 Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3,

	604292 Hay-Wells syndrome, 106260 Limb-mammary syndrome, 603543 Split-hand/foot malformation, type 4, 605289
603284	Cerebral cavernous malformations-2
603285	Cerebral cavernous malformations-3
603324	Deafness, autosomal dominant 2, 600101 Deafness, autosomal dominant, with peripheral neuropathy Deafness, autosomal recessive Erythrokeratodermia variabilis, 133200
603490	XY female
603590	Meningioma
603593	Lysinuric protein intolerance, 222700
603688	Prostate cancer-brain cancer susceptibility
603776	Hypercholesterolemia, familial, 3
603945	Leukoencephalopathy with vanishing white matter, 603896
603959	Hypomagnesemia, primary, 248250
603967	Cramps, familial, potassium-aggravated Hyperkalemic periodic paralysis, 170500 Hypokalemic periodic paralysis, 170400 Myotonia congenita, atypical, acetazolamide-responsive, 170500 Paramyotonia congenita, 168300
604365	Retinal degeneration, autosomal recessive, prominin-related
604484	Neuropathy, hereditary motor and sensory, Okinawa type
604630	Obesity, mild, early-onset, 601665
604763	Leukemia, acute myeloid
604802	Huntington disease-like 3
604831	Ellis-van Creveld syndrome, 225500 Weyers acrodental dysostosis, 193530
604933	Adenomatous polyposis of the colon, susceptibility to, 175100
605201	Hypoalphalipoproteinemia, primary
605225	Inflammatory bowel disease-7, 266600
605229	Spastic paraplegia 14, autosomal recessive
605389	Hypotrichosis simplex
605425	Erythrokeratodermia variabilis with erythema gyratum repens, 133200
605441	Adiponectin deficiency
605463	Radiation sensitivity/chromosome instability syndrome, autosomal dominant
605480	Systemic lupus erythematosus, susceptibility to, 3, 152700
605543	Parkinson disease 4, autosomal dominant, Lewy body
605552	Abdominal obesity-metabolic syndrome
605747	Hypercholesterolemia, familial, autosomal recessive, 603813
605841	Narcolepsy, 161400
605909	Parkinson disease, 168600
605995	Charcot-Marie-Tooth neuropathy, type 2A, 118210

606210	Muscular dystrophy, rigid spine, 1, 602771
606224	Anemia, hemolytic, due to UMPH1 deficiency, 266120
606246	Endometrial stromal tumors
606324	Parkinson disease, 168600
606439	Spastic paraplegia-3A, 182600
606675	Inflammatory bowel disease-4, 266600
606693	Kufor-Rakeb syndrome
606800	Glycogen storage disease II, 232300
606811	Hyperprolinemia, type II, 239510
606860	Angioedema, hereditary, 106100
606928	[Bone mineral density variability 3], 601884
606953	Galactose epimerase deficiency, 230350
606996	Senior-Loken syndrome 4
607037	Peroxisomal bifunctional enzyme deficiency, 261515
607086	Aortic aneurysm, familial thoracic 1
607093	Homocystinuria due to MTHFR deficiency, 236250
607107	Nasopharyngeal carcinoma 1, 161550
607215	Nephronophthisis 4, 606966

[1166] Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

EXAMPLES

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

[1167] Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

Vector Used to Construct Library	Corresponding Deposited Plasmid
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSport 2.0	pCMVSport 2.0
pCMVSport 3.0	pCMVSport 3.0
pCR®2.1	pCR®2.1

[1168] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short et al., *Nucleic Acids Res.*, 16:7583-7600 (1988); Alting-Mees et al., *Nucleic Acids Res.*, 17:9494 (1989)) and pBK (Alting-Mees et al., *Strategies*, 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single

stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

[1169] Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993)). Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, *Nuc. Acids Res.*, 16:9677-9686 (1988) and Mead et al., *Bio/Technology*, 9 (1991)). Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

[1170] The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA Plasmid:V identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

[1171] Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

[1172] Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982)). The plasmid

mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

[1173] Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

[1174] Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.*, 21(7):1683-1684 (1993)).

[1175] Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known

sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

[1176] This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

[1177] This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

[1178] A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

[1179] Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P^{32} using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

[1180] Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

Example 4: Chromosomal Mapping of the Polynucleotides

[1181] An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

[1182] A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI and initiation/stop codons, if necessary, to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

[1183] The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial

RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

[1184] Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 ($O.D.^{600}$) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

[1185] Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

[1186] Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

[1187] The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4° C or frozen at -80° C.

[1188] In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

[1189] DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

[1190] The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

[1191] The following alternative method can be used to purify a polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

[1192] Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

[1193] The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by

centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

[1194] The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

[1195] Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

[1196] To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

[1197] Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

[1198] The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 μg of purified protein is loaded.

The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

[1199] In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

[1200] Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

[1201] Specifically, the cDNA sequence contained in the deposited clone is amplified using the PCR protocol described in Example 1 using primers with appropriate restriction sites and initiation/stop codons. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin NO: 1555 (1987).

[1202] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[1203] The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

[1204] The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

[1205] Five μg of a plasmid containing the polynucleotide is co-transfected with 1.0 μg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μg of BaculoGold™ virus DNA and 5 μg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μl Lipofectin plus 90 μl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

[1206] After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 μl of Grace's medium and the suspension containing

the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

[1207] To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 μCi of ^{35}S-methionine and 5 μCi ^{35}S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

[1208] Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

[1209] The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

[1210] Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

[1211] Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable

marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

[1212] The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt et al., *J. Biol. Chem.*, 253:1357-1370 (1978); Hamlin et al., *Biochem. et Biophys. Acta*, 1097:107-143 (1990); Page et al., *Biotechnology*, 9:64-68 (1991)). Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., *Biochem J.*, 227:277-279 (1991); Bebbington et al., *Bio/Technology*, 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

[1213] Derivatives of the plasmid pSV2-dhfr (ATCC Accession No.: 37146), the expression vectors pC4 (ATCC Accession No.: 209646) and pC6 (ATCC Accession No.:209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., *Molecular and Cellular Biology*, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., *Cell*, 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

[1214] Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

[1215] A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1 using primers with appropriate restrictions sites and initiation/stop codons, if necessary. The vector can be modified to include a heterologous signal sequence if necessary for secretion. (See, e.g., WO 96/34891.)

[1216] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[1217] The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

[1218] Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pC6 is cotransfected with 0.5 μg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μM, 2 μM, 5 μM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

[1219] The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., *Nature*, 331:84-86 (1988)) The polypeptides can also be fused to heterologous polypeptide sequences to facilitate secretion and intracellular trafficking (e.g., KDEL). Moreover, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or

homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

[1220] Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector, and initiation/stop codons, if necessary.

[1221] For example, if pC4 (Accession No.: 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

[1222] If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

<u>Human IgG Fc region:</u>

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAT
TCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG
GACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAA
CTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACA
ACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGG
AGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAG
CCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCA
AGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC

TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT CTCCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

Example 10: Formulating a Polypeptide

[1223] The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By Therapeutic is meant polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

[1224] The polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

[1225] As a general proposition, the total pharmaceutically effective amount of polypeptide administered parenterally per dose will be in the range of about 1 μg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the polypeptide is typically administered at a dose rate of about 1 μg/kg/hour to about 50 μg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

[1226] Pharmaceutical compositions containing the polypeptide of the invention are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any

type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

[1227] The polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules. Sustained-release matrices include polylactides (U.S. Pat. NO: 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., *Biopolymers*, 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and Langer, *Chem. Tech.*, 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

[1228] In a preferred embodiment, compositions of the invention are formulated in a biodegradable, polymeric drug delivery system, for example as described in U.S. Patent Nos. 4,938,763; 5,278,201; 5,278,202; 5,324,519; 5,340,849; and 5,487,897 and in International Publication Numbers WO01/35929, WO00/24374, and WO00/06117 which are hereby incorporated by reference in their entirety. In specific preferred embodiments the compositions of the invention are formulated using the ATRIGEL® Biodegradable System of Atrix Laboratories, Inc. (Fort Collins, Colorado).

[1229] Examples of biodegradable polymers which can be used in the formulation of compositions of the invention include, but are not limited to, polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures of the above materials. The preferred polymers are those that have a lower degree of crystallization and are more hydrophobic. These polymers and copolymers are more soluble in the biocompatible solvents than the highly crystalline polymers such as polyglycolide and chitin which also have a high degree of hydrogen-bonding. Preferred materials with the desired solubility parameters are the polylactides, polycaprolactones, and copolymers of these with glycolide in which there are more

amorphous regions to enhance solubility. In specific preferred embodiments, the biodegradable polymers which can be used in the formulation of compositions of the invention are poly(lactide-co-glycolides). Polymer properties such as molecular weight, hydrophobicity, and lactide/glycolide ratio may be modified to obtain the desired drug release profile (See, e.g., Ravivarapu et al., Journal of Pharmaceutical Sciences 89:732-741 (2000), which is hereby incorporated by reference in its entirety).

[1230] It is also preferred that the solvent for the biodegradable polymer be non-toxic, water miscible, and otherwise biocompatible. Examples of such solvents include, but are not limted to, N-methyl-2-pyrrolidone, 2-pyrrolidone, C2 to C6 alkanols, C1 to C15 alchohols, dils, triols, and tetraols such as ethanol, glycerine propylene glycol, butanol; C3 to C15 alkyl ketones such as acetone, diethyl ketone and methyl ethyl ketone; C3 to C15 esters such as methyl acetate, ethyl acetate, ethyl lactate; alkyl ketones such as methyl ethyl ketone, C1 to C15 amides such as dimethylformamide, dimethylacetamide and caprolactam; C3 to C20 ethers such as tetrahydrofuran, or solketal; tweens, triacetin, propylene carbonate, decylmethylsulfoxide, dimethyl sulfoxide, oleic acid, 1-dodecylazacycloheptan-2-one, Other preferred solvents are benzyl alchohol, benzyl benzoate, dipropylene glycol, tributyrin, ethyl oleate, glycerin, glycofural, isopropyl myristate, isopropyl palmitate, oleic acid, polyethylene glycol, propylene carbonate, and triethyl citrate. The most preferred solvents are N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, triacetin, and propylene carbonate because of the solvating ability and their compatibility.

[1231] Additionally, formulations comprising compositions of the invention and a biodegradable polymer may also include release-rate modification agents and/or pore-forming agents. Examples of release-rate modification agents include, but are not limited to, fatty acids, triglycerides, other like hydrophobic compounds, organic solvents, plasticizing compounds and hydrophilic compounds. Suitable release rate modification agents include, for example, esters of mono-, di-, and tricarboxylic acids, such as 2-ethoxyethyl acetate, methyl acetate, ethyl acetate, diethyl phthalate, dimethyl phthalate, dibutyl phthalate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, glycerol triacetate, di(n-butyl) sebecate, and the like; polyhydroxy alcohols, such as propylene glycol, polyethylene glycol, glycerin, sorbitol, and the like; fatty acids; triesters of glycerol, such as

triglycerides, epoxidized soybean oil, and other epoxidized vegetable oils; sterols, such as cholesterol; alcohols, such as C.sub.6 -C.sub.12 alkanols, 2-ethoxyethanol, and the like. The release rate modification agent may be used singly or in combination with other such agents. Suitable combinations of release rate modification agents include, but are not limited to, glycerin/propylene glycol, sorbitol/glycerine, ethylene oxide/propylene oxide, butylene glycol/adipic acid, and the like. Preferred release rate modification agents include, but are not limited to, dimethyl citrate, triethyl citrate, ethyl heptanoate, glycerin, and hexanediol. Suitable pore-forming agents that may be used in the polymer composition include, but are not limited to, sugars such as sucrose and dextrose, salts such as sodium chloride and sodium carbonate, polymers such as hydroxylpropylcellulose, carboxymethylcellulose, polyethylene glycol, and polyvinylpyrrolidone. Solid crystals that will provide a defined pore size, such as salt or sugar, are preferred.

[1232] In specific preferred embodiments the compositions of the invention are formulated using the BEMA™ BioErodible Mucoadhesive System, MCA™ MucoCutaneous Absorption System, SMP™ Solvent MicroParticle System, or BCP™ BioCompatible Polymer System of Atrix Laboratories, Inc. (Fort Collins, Colorado).

[1233] Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. USA*, 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci. USA* , 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

[1234] For parenteral administration, in one embodiment, the polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

[1235] Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

[1236] The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

[1237] The polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

[1238] Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[1239] Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is

lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

[1240] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

[1241] The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable prepartions of *Corynebacterium parvum*. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[1242] The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. In preferred embodiments, therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to antidiabetic agents (e.g., a biguanide antidiabetic agent, a glitazone antidiabetic agent, and a sulfonylurea antidiabetic agent). In additional embodiments, therapeutic agents that may be administered in combination with the Therapeutics of the invention, include chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[1243] In one embodiment, the Therapeutics of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the compositions of the invention include, but are not limited to, heparin, low molecular weight heparin, warfarin sodium (e.g., COUMADIN®), dicumarol, 4-hydroxycoumarin, anisindione (e.g., MIRADON™), acenocoumarol (e.g., nicoumalone, SINTHROME™), indan-1,3-dione, phenprocoumon (e.g., MARCUMAR™), ethyl biscoumacetate (e.g., TROMEXAN™), and aspirin. In a specific embodiment, compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, compositions of the invention are administered in combination with heparin. In another specific embodiment, compositions of the invention are administered in combination with heparin and aspirin.

[1244] In another embodiment, the Therapeutics of the invention are administered in combination with thrombolytic drugs. Thrombolytic drugs that may be administered with the compositions of the invention include, but are not limited to, plasminogen, lys-

plasminogen, alpha2-antiplasmin, streptokinae (e.g., KABIKINASE™), antiresplace (e.g., EMINASE™), tissue plasminogen activator (t-PA, altevase, ACTIVASE™), urokinase (e.g., ABBOKINASE™), sauruplase, (Prourokinase, single chain urokinase), and aminocaproic acid (e.g., AMICAR™). In a specific embodiment, compositions of the invention are administered in combination with tissue plasminogen activator and aspirin.

[1245] In another embodiment, the Therapeutics of the invention are administered in combination with antiplatelet drugs. Antiplatelet drugs that may be administered with the compositions of the invention include, but are not limited to, aspirin, dipyridamole (e.g., PERSANTINE™), and ticlopidine (e.g., TICLID™).

[1246] In specific embodiments, the use of anti-coagulants, thrombolytic and/or antiplatelet drugs in combination with Therapeutics of the invention is contemplated for the prevention, diagnosis, and/or treatment of thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the use of anticoagulants, thrombolytic drugs and/or antiplatelet drugs in combination with Therapeutics of the invention is contemplated for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the therapeutics of the invention, alone or in combination with antiplatelet, anticoagulant, and/or thrombolytic drugs, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[1247] In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the

Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

[1248] Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott; COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead); DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of β-L-FD4C and β-L-FddC (WO 98/17281).

[1249] Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and Propolis (WO 99/49830).

[1250] Additional protease inhibitors include LOPINAVIR™ (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myres Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity against protease inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Welcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

[1251] Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

[1252] Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine recpetor agonists such as RANTES, SDF-1, MIP-1α, MIP-1β, etc., may also inhibit fusion.

[1253] Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones; ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

[1254] Additional antiretroviral agents include hydroxyurea-like compunds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate

dehydrogenase (IMPDH) inhibitors sucha as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

[1255] Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

[1256] Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1α, MIP-1β, SDF-1α, IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN-α2a; antagonists of TNFs, NFκB, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targetted to the ER to block surface expression of newly synthesized CCR5 (Yang *et al., PNAS 94*:11567-72 (1997); Chen *et al., Nat. Med. 3*:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF-α antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and α-naphthoflavone (WO 98/30213); and antioxidants such as γ-L-glutamyl-L-cysteine ethyl ester (γ-GCE; WO 99/56764).

[1257] In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the

Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

[1258] In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with

PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

[1259] In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

[1260] In other embodiments, the Therapeutics of the invention are administered in combination with immunestimulants. Immunostimulants that may be administered in combination with the Therapeutics of the invention include, but are not limited to, levamisole (e.g., ERGAMISOL™), isoprinosine (e.g. INOSIPLEX™), interferons (e.g. interferon alpha), and interleukins (e.g., IL-2).

[1261] In other embodiments, Therapeutics of the invention are administered in combination with immunosuppressive agents. Immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate motefil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™

(methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

[1262] In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™ (antithymocyte glubulin), and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

[1263] In certain embodiments, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

[1264] In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of

Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[1265] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[1266] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[1267] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[1268] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-

propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

[1269] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolmidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

[1270] Anti-angiogenic agents that may be administed in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositons of the invention include, but are not lmited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb,

Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositons of the invention include, but are not lmited to, EMD-121974 (Merck KcgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositons of the invention include, but are not lmited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositons of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

[1271] In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

[1272] In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

[1273] In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth

factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

[1274] In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcolysin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouacil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone proprionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing horomone analogs (for example, Leuprolide), other hormones and hormone analogs (for example,

methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

[1275] In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

[1276] In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with tositumomab. In a further embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

[1277] In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more radisotopes. Particularly preferred isotopes are ^{90}Y and ^{111}In.

[1278] In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics

of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

[1279] In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

[1280] In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International

Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

[1281] In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

[1282] In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

[1283] In certain embodiments, Therapeutics of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

[1284] In another embodiment, the Therapeutics of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amidoarone, bretylium, digitalis, digoxin, digitoxin, diliazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

[1285] In another embodiment, the Therapeutics of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorphenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit Na^+-K^+-$2Cl^-$ symport (e.g., furosemide, bumetanide, azosemide, piretanide, tripamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

[1286] In one embodiment, the Therapeutics of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, ^{127}I, radioactive isotopes of iodine such as ^{131}I and ^{123}I; recombinant growth hormone, such as HUMATROPE™ (recombinant somatropin); growth hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T_4™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T_3™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-*n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™

(carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca^{2+} channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).

[1287] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or congugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone), LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

[1288] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone

enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotropic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate),

HALDRONE™ (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone);

[1289] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), PRECOSE™ (acarbose), AMARYL™ (glimepiride), and ciglitazone; thiazolidinediones (TZDs) such as rosiglitazone, AVANDIA™ (rosiglitazone maleate) ACTOS™ (piogliatazone), and troglitazone; alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide). In still other embodiments, Therapeutics of the invention are administered in combination with one or more of the following: a biguanide antidiabetic agent, a glitazone antidiabetic agent, and a sulfonylurea antidiabetic agent.

[1290] In one embodiment, the Therapeutics of the invention are administered in combination with treatments for uterine motility disorders. Treatments for uterine motility disorders include, but are not limited to, estrogen drugs such as conjugated estrogens (e.g., PREMARIN® and ESTRATAB®), estradiols (e.g., CLIMARA® and ALORA®), estropipate, and chlorotrianisene; progestin drugs (e.g., AMEN® (medroxyprogesterone), MICRONOR® (norethidrone acetate), PROMETRIUM® progesterone, and megestrol acetate); and estrogen/progesterone combination therapies such as, for example,

conjugated estrogens/medroxyprogesterone (e.g., PREMPRO™ and PREMPHASE®) and norethindrone acetate/ethinyl estsradiol (e.g., FEMHRT™).

[1291] In an additional embodiment, the Therapeutics of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL™), ferrous fumarate (e.g., FEOSTAT™), ferrous gluconate (e.g., FERGON™), polysaccharide-iron complex (e.g., NIFEREX™), iron dextran injection (e.g., INFED™), cupric sulfate, pyroxidine, riboflavin, Vitamin B_{12}, cyancobalamin injection (e.g., REDISOL™, RUBRAMIN PC™), hydroxocobalamin, folic acid (e.g., FOLVITE™), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

[1292] In certain embodiments, the Therapeutics of the invention are administered in combination with agents used to treat psychiatric disorders. Psychiatric drugs that may be administered with the Therapeutics of the invention include, but are not limited to, antipsychotic agents (e.g., chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and triflupromazine), antimanic agents (e.g., carbamazepine, divalproex sodium, lithium carbonate, and lithium citrate), antidepressants (e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, fluvoxamine, fluoxetine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine), antianxiety agents (e.g., alprazolam, buspirone, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam), and stimulants (e.g., d-amphetamine, methylphenidate, and pemoline).

[1293] In other embodiments, the Therapeutics of the invention are administered in combination with agents used to treat neurological disorders. Neurological agents that may be administered with the Therapeutics of the invention include, but are not limited to, antiepileptic agents (e.g., carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproic acid, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, diazepam, lorazepam, and clonazepam), antiparkinsonian agents (e.g., levodopa/carbidopa,

selegiline, amantidine, bromocriptine, pergolide, ropinirole, pramipexole, benztropine; biperiden; ethopropazine; procyclidine; trihexyphenidyl, tolcapone), and ALS therapeutics (e.g. riluzole).

[1294] In another embodiment, Therapeutics of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents. Vasodilating agents that may be administered with the Therapeutics of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

[1295] In certain embodiments, the Therapeutics of the invention are administered in combination with treatments for gastrointestinal disorders. Treatments for gastrointestinal disorders that may be administered with the Therapeutic of the invention include, but are not limited to, H_2 histamine receptor antagonists (e.g., TAGAMET™ (cimetidine), ZANTAC™ (ranitidine), PEPCID™ (famotidine), and AXID™ (nizatidine)); inhibitors of H^+, K^+ ATPase (e.g., PREVACID™ (lansoprazole) and PRILOSEC™ (omeprazole)); Bismuth compounds (e.g., PEPTO-BISMOL™ (bismuth subsalicylate) and DE-NOL™ (bismuth subcitrate)); various antacids; sucralfate; prostaglandin analogs (e.g. CYTOTEC™ (misoprostol)); muscarinic cholinergic antagonists; laxatives (e.g., surfactant laxatives, stimulant laxatives, saline and osmotic laxatives); antidiarrheal agents (e.g., LOMOTIL™ (diphenoxylate), MOTOFEN™ (diphenoxin), and IMODIUM™ (loperamide hydrochloride)), synthetic analogs of somatostatin such as SANDOSTATIN™ (octreotide), antiemetic agents (e.g., ZOFRAN™ (ondansetron), KYTRIL™ (granisetron hydrochloride), tropisetron, dolasetron, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, triflupromazine, domperidone, haloperidol, droperidol, trimethobenzamide, dexamethasone, methylprednisolone, dronabinol, and nabilone); D2 antagonists (e.g., metoclopramide, trimethobenzamide and chlorpromazine); bile salts; chenodeoxycholic

acid; ursodeoxycholic acid; and pancreatic enzyme preparations such as pancreatin and pancrelipase.

[1296] In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Example 11: Method of Treating Decreased Levels of the Polypeptide

[1297] It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted and/or soluble form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

[1298] For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 10.

Example 12: Method of Treating Increased Levels of the Polypeptide

[1299] Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

[1300] For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The antisense polynucleotides of the present invention can be formulated using techniques and formulations described herein (e.g., see Example 10) or otherwise known in the art.

Example 13: Method of Treatment Using Gene Therapy - Ex Vivo

[1301] One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

[1302] At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

[1303] pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

[1304] The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

[1305] The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then

added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

[1306] Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

[1307] The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 14: Gene Therapy Using Endogenous ACRP30-Like Genes

[1308] Another method of gene therapy according to the present invention involves operably associating the endogenous ACRP30-Like gene sequence with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA,* 86:8932-8935 (1989); and Zijlstra et al., *Nature,* 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

[1309] Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of the endogenous ACRP30-Like gene, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the ACRP30-Like gene so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting

sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

[1310] The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

[1311] In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

[1312] Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous ACRP30-Like gene sequence. This results in the expression of ACRP30-Like polypeptides in the cell. Expression may be detected by immunological staining, or any other method known in the art.

[1313] Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na_2HPO_4, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately $3X10^6$ cells/ml. Electroporation should be performed immediately following resuspension.

[1314] Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the ACRP30-Like locus, plasmid pUC18 (MBI

Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3'end. Two ACRP30-Like non-coding gene sequences are amplified via PCR: one ACRP30-Like non-coding sequence (ACRP30-Like fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3'end; the other ACRP30-Like non-coding sequence (ACRP30-Like fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and ACRP30-Like fragments are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; ACRP30-Like fragment 1 - XbaI; ACRP30-Like fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

[1315] Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 μg/ml. 0.5 ml of the cell suspension (containing approximately $1.5.X10^6$ cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μF and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

[1316] Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

[1317] The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 15: Method of Treatment Using Gene Therapy - In Vivo

[1318] Another aspect of the present invention is using *in vivo* gene therapy methods

to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) ACRP30-Like sequences into an animal to increase or decrease the expression of the ACRP30-Like polypeptide. The ACRP30-Like polynucleotide may be operatively linked to a promoter or any other genetic elements necessary for the expression of the ACRP30-Like polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO: 5693622, 5705151, 5580859; Tabata et al., *Cardiovasc. Res.* 35(3):470-479 (1997), Chao J et al., *Pharmacol. Res.*, 35(6):517-522 (1997), Wolff, *Neuromuscul. Disord.* 7(5):314-318 (1997), Schwartz et al., *Gene Ther.*, 3(5):405-411 (1996), Tsurumi Y. et al., *Circulation*, 94(12):3281-3290 (1996) (incorporated herein by reference).

[1319] The ACRP30-Like polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The ACRP30-Like polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[1320] The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the ACRP30-Like polynucleotides may also be delivered in liposome formulations (such as those taught in Felgner et al., *Ann. NY Acad. Sci.*, 772:126-139 (1995) and Abdallah et al., *Biol. Cell* , 85(1):1-7 (1995)) which can be prepared by methods well known to those skilled in the art.

[1321] The ACRP30-Like polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[1322] The polynucleotide constructs can be delivered to the interstitial space of tissues

within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[1323] For the naked ACRP30-Like polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked ACRP30-Like polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[1324] The dose response effects of injected ACRP30-Like polynucleotide in muscle *in vivo* is determined as follows. Suitable ACRP30-Like template DNA for production of mRNA coding for ACRP30-Like polypeptide is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or

linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

[1325] Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The ACRP30-Like template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

[1326] After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for ACRP30-Like protein expression. A time course for ACRP30-Like protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of ACRP30-Like DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using ACRP30-Like naked DNA.

Example 16: Production of an Antibody

a) Hybridoma Technology

[1327] The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing ACRP30-Like polypeptide(s) are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of ACRP30-Like polypeptide(s) is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

[1328] Monoclonal antibodies specific for ACRP30-Like polypeptide(s) are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J.

Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with ACRP30-Like polypeptide(s) or, more preferably, with a secreted ACRP30-Like polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 μg/ml of streptomycin.

[1329] The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the ACRP30-Like polypeptide(s).

[1330] Alternatively, additional antibodies capable of binding to ACRP30-Like polypeptide(s) can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the ACRP30-Like protein-specific antibody can be blocked by ACRP30-Like polypeptide(s). Such antibodies comprise anti-idiotypic antibodies to the ACRP30-Like protein-specific antibody and are used to immunize an animal to induce formation of further ACRP30-Like protein-specific antibodies.

[1331] For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al.,

U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985)).

b) Isolation Of Antibody Fragments Directed Against ACRP30-Like Polypeptide(s) From A Library Of scFvs

[1332] Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against ACRP30-Like polypeptide(s) to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library.

[1333] A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 109 E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 μg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to innoculate 50 ml of 2xTY-AMP-GLU, 2 x 108 TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 μg/ml ampicillin and 50 μg/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

[1334] M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium

by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately 1013 transducing units/ml (ampicillin-resistant clones).

Panning of the Library.

[1335] Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 1013 TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders.

[1336] Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 17: [^{3}H]-2-Deoxyglucose Uptake Assay

[1337] Adipose, skeletal muscle, and liver are insulin-sensitive tissues. Insulin can stimulate glucose uptake/transport into these tissues. In the case of adipose and skeletal muscle, insulin initiates the signal transduction that eventually leads to the translocation of GLUT4, the glucose transporter 4 molecule, from a specialized intracellular compartment to the cell surface. Once on the cell surface, GLUT4 allows for glucose uptake/transport.

[1338] A number of adipose and muscle related cell-lines can be used to test for glucose uptake/transport activity in the presence of an ACRP-30 Like polypeptide of the invention. In particular, the 3T3-L1 murine fibroblast cells and the L6 murine skeletal muscle cells can be differentiated into 3T3-L1 adipocytes and into myotubes, respectively, to serve as appropriate *in vitro* models for the ^{3}H-2-deoxyglucose uptake assay (Haspel et al., 1999, J Membr Biol, 169 (1): 45-53; Tsakiridis et al., 1995, Endocrinology, 136(10): 4315-22). Briefly, 2 x 10^{5} cells/100 uL of adipocytes or differentiated L6 cells are transferred to 96-well Tissue-Culture, "TC", treated, i.e. coated with 50 ug/mL of poly-L-lysine, plates for 4 hours at 37 °C. The cells are washed once with HEPES buffered saline. Insulin, or an ACRP-30 Like polypeptide, is added at various dilutions (e.g., 5 nM, 10 nM, 100 nM, and 500 nM for insulin) in HEPES buffered saline for 30 min at 37 °C. A final concentration of 10 uM cytochalasin B is added to measure the non-specific uptake. The cells are washed three times with HEPES buffered saline. Labeled, i.e. 10 uM of [^{3}H]-2-deoxyglucose, and unlabeled, i.e. 2-deoxyglucose, are added for 10 minutes at room temperature. The cells are washed three times with cold Phosphate Buffered Saline, "PBS". The cells are lysed upon the addition of 150 uL/well of 0.05 N NaOH and subsequent incubation with shaking for 20 minutes at room temperature. Samples are then transferred to a scintillation vial to which is added 5 mL of scintillation fluid. The vials are counted in a Beta-Scintillation counter. Maximal responses of about 5-fold and 3-fold that of controls for adipocytes and myotubes, respectively, are to be expected.

[1339] It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[1340] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties.

[1341] Certain ACRP-30-Like polynucleotides and polypeptides of the present invention, including antibodies, were disclosed in U.S. provisional application number 60/328,419, filed October 12, 2001, the specification and sequence listing of which are herein incorporated by reference in their entireties.

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Date of deposit	Accession Number
August 13, 1999	PTA-536

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. PTA-536

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: PTA-536

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on Page 181, Table 1.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
September 10, 2001	PTA-3696

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. PTA-3696

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: PTA-3696

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on Page 181, Table 1.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
October 5, 2000	PTA-2574

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. PTA-2574

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: PTA-2574

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on Page 181, Table 1.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
October 5, 2000	PTA-2575

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. PTA-2575

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: PTA-2575

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on Page 182, Table 1.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
July 27, 1998	203071

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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ATCC Deposit No. 203071

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 203071

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on Page 182, Table 1.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
June 19, 1997	209124

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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ATCC Deposit No. 209124

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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ATCC Deposit No.: 209124

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on Page 182, Table 1.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
September 27, 1999	PTA-791

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
☑ This sheet was received with the international application 11 OCT 2002	☐ This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

Revised Form PCT/RO/134 (January 2001) Pctro134ep.sollist

ATCC Deposit No. PTA-791

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: PTA-791

UNITED KINGDOM

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10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
June 11, 2001	PTA-3449

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

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For receiving Office use only	For International Bureau use only
☑ This sheet was received with the international application 11 OCT 2002	☐ This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

Revised Form PCT/RO/134 (January 2001) Pctro134ep.sollist

ATCC Deposit No. PTA-3449

CANADA

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ATCC Deposit No.: PTA-3449

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CLAIMS

We claim:

1. An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:

(a) the polynucleotide shown as SEQ ID NO:X or the polynucleotide encoded by a cDNA included in ATCC Deposit No:Z;

(b) a polynucleotide encoding a biologically active polypeptide fragment of SEQ ID NO:Y or a biologically active polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z;

(c) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z;

(d) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(c), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide comprises a nucleotide sequence encoding a soluble polypeptide.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide comprises the entire nucleotide sequence of SEQ ID NO:X or a cDNA included in ATCC Deposit No:Z.

5. The isolated nucleic acid molecule of claim 2, wherein the polynucleotide is DNA.

6. The isolated nucleic acid molecule of claim 3, wherein the polynucleotide is RNA.

7. A vector comprising the isolated nucleic acid molecule of claim 1.

8. A host cell comprising the vector of claim 7.

9. A recombinant host cell comprising the nucleic acid molecule of claim 1 operably limited to a heterologous regulating element which controls gene expression.

10. A method of producing a polypeptide comprising expressing the encoded polypeptide from the host cell of claim 9 and recovering said polypeptide.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) the polypeptide shown as SEQ ID NO:Y or the polypeptide encoded by the cDNA;

(b) a polypeptide fragment of SEQ ID NO:Y or the polypeptide encoded by the cDNA;

(c) a polypeptide epitope of SEQ ID NO:Y or the polypeptide encoded by the cDNA; and

(d) a variant of SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, comprising a polypeptide having SEQ ID NO:Y.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. A method of screening for molecules which modify activities of the polypeptide of claim 11 comprising:

(a) contacting said polypeptide with a compound suspected of having agonist or antagonist activity; and

(b) assaying for activity of said polypeptide.

22. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount the polypeptide of claim 11.

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tgctgtctga gcatccaggc ccaaaggcac tgagggagtc aggagctggg gctcggcaca   1620
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ccaggccctc ccgcatctca ggttggggat ggggacatgg agaggaaggg gccgcctact   1860
cctgcaaatg cttgtgacag atgccaggag gtagatgtgt gctggccaat aaaggcccct   1920
acctgattcc ccgcaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa   1980
aaaaaaaaaa aaaaaaaaaa aaaaaaa                                       2007
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<210> 4
<211> 901
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (872)..(872)
<223> n equals a,t,g, or c

<400> 4

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cggtccccca ggacctccag gtgcagaagt gaccgcggag actctgcttc acgagtttca    180
ggagctgctg aaagaggcca cggagcgccg gttctcaggg cttctggacc cgctgctgcc    240
ccaggggggcg ggcctgcggc tggtgggcga ggcctttcac tgccggctgc agggtccccg    300
ccgggtggac aagcggacgc tggtggagct gcatggtttc caggctcctg ctgcccaagg    360
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gtgagggcgc ccaggggggc tggcgaggag ctgccgccgg atcccgggga ccctcctact    780
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g                                                                   901
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<210> 5
<211> 1558
<212> DNA
<213> Homo sapiens

<400> 5

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cactgccgtc ctccggaaga ccttttcccc tgctctgttt ccttcaccga gtctgtgcat    180
cgcccccggac ctggccggga ggaggcttgg ccggcgggag atgctctagg ggcggcgcgg    240
gaggagcggc cggcgggacg gagggcccgg caggaagatg ggctcccgtg gacagggact    300
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<210> 6
<211> 1313
<212> DNA
<213> Homo sapiens

<400> 6
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ttctggtgct tctggccctg ggggccgggt gggcccagga ggggtcagag cccgtcctgc    240
tggaggggga gtgcctggtg gtctgtgagc ctggccgagc tgctgcaggg gggcccgggg    300
gagcagccct gggagaggca ccccctgggc gagtggcatt tgctgcggtc cgaagccacc    360
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<210> 7
<211> 1312
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (27)..(27)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1204)..(1204)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1225)..(1225)
<223> n equals a,t,g, or c

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cggcgccgtc acctcctccc taggcatctc cgtgcgctcc ggcagcgcca aggtggcctt    180
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gtanttgttt gtgtttttc cttgnaaaag ctttactttt cctttccaca ctcagctctt 1260
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<210> 8
<211> 1022
<212> DNA
<213> Homo sapiens

<400> 8
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<211> 1254
<212> DNA
<213> Homo sapiens

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ttttcaagta ttggaagggg tggggagata tataaataaa tcatgaaatc aataaaaaaa 1140
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1200
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 1254

<210> 10
<211> 1618
<212> DNA
<213> Homo sapiens

<400> 10
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<210> 11
<211> 1336
<212> DNA
<213> Homo sapiens

<400> 11
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<210> 12
<211> 1114
<212> DNA
<213> Homo sapiens

<400> 12
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<210> 13
<211> 659
<212> DNA
<213> Homo sapiens

<400> 13

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<210> 14
<211> 1195
<212> DNA
<213> Homo sapiens

<220>
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<223> n equals a,t,g, or c

<400> 14

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<211> 3951
<212> DNA
<213> Homo sapiens

<220>
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<222> (3871)..(3871)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (3903)..(3903)
<223> n equals a,t,g, or c

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<211> 1280
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1271)..(1271)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1279)..(1279)
<223> n equals a,t,g, or c

<400> 16

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aaagggataa tttccagcag tgttataagc gaggagggac atctggtggt ccacgagcaa    240
attcgagagc taactgcttc attatgagaa actcactgtt gctaataaaa cagcagggtg    300
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aaaaaaaaaa nggggggggnc                                              1280
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<210> 17
<211> 3764
<212> DNA
<213> Homo sapiens

<400> 17
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<210> 18
<211> 2485

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<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2415)..(2415)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2425)..(2425)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2481)..(2481)
<223> n equals a,t,g, or c

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<210> 19
<211> 1550
<212> DNA
<213> Homo sapiens

<220>
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<222> (1547)..(1547)
<223> n equals a,t,g, or c

<400> 19
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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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<211> 3522
<212> DNA
<213> Homo sapiens

<400> 23

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<211> 1969
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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tctgtgaagt gggggaggc aggccttcaa ggagggatag aggtacaagg cttcgtctca     1560
tctgctgtct gagcatccag gcccaaaggc actgagggag tcaggagctg ggctcggca     1620
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gctgcccaat cctctgactg gatcaccggg ggcttcttgc ctcagttctt ccctctgagc    1800
ccccaggccc tcccgcatct caggttgggg atggggacat ggagaggaag gggccgccta    1860
ctcctgcaaa tgcttgtgac agatgccagg aggtagatgt gtgctggcca ataaaggccc    1920
ctacctgatt ccccgcaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaa                1969
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<210> 25
<211> 2189
<212> DNA
<213> Homo sapiens

<220>
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<222> (2)..(2)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (4)..(4)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (7)..(7)
<223> n equals a,t,g, or c

<400> 25

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gggcttgggc gctgctctgc ctcgggctcc tgctcccggg aggcggcgct gcgtggagca     180
tcggggcagc tccgttctcc ggacgcagga actggtgctc ctatgtggtg acccgcacca     240
tctcatgcca tgtgcagaat ggcacctacc ttcagcgagt gctgcagaac tgcccctggc     300
ccatgagctg tccggggagc agctacagaa ctgtggtgag acccacatac aaggtgatgt     360
acaagatagt gaccgcccgt gagtggaggt gctgccctgg gcactcagga gtgagctgcg     420
aggaagttgc agcttcctct gcctccttgg agcccatgtg gtcgggcagt accatgcggc     480
ggatggcgct tcggcccaca gccttctcag gttgtctcaa ctgcagcaaa gtgtcagagc     540
tgacagagcg gctgaaggtg ctggaggcca agatgaccat gctgactgtc atagagcagc     600
cagtacctcc aacaccagct acccctgagg accctgcccc gctctggggt ccccctcctg     660
cccagggcag ccccggagat ggaggcctcc aggaccaagt cggtgcttgg gggcttcccg     720
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ggcccaccgg ccccaaggga gatgccggca gtcggggccc aatggggatg agaggcccac     780
caggtccaca gggcccccca gggagccctg gccgggctgg agctgtgggc acccctggag     840
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caggccccac tggacccaaa ggaatctctg gccacccagg agagaagggc gagagaggac    1140
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<210> 26
<211> 1236
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> n equals a,t,g, or c

<220>
<221> misc_feature

<222> (6)..(6)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (14)..(14)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (27)..(27)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (39)..(39)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1230)..(1230)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1232)..(1233)
<223> n equals a,t,g, or c
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<220>
<221> misc_feature
<222> (1236)..(1236)
<223> n equals a,t,g, or c

<400> 26
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cctgggcact caggagtgag ctgcgaggaa gttgcagctt cctctgcctc cttggagccc 240
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ggcccaatgg ggatgagagg cccaccaggt ccacagggcc ccccagggag ccctggccgg 600
gctggagctg tgggcacccc tggagagagg ggacctcckg ggccaccagg gcctcctggc 660
ccccctgggc ccccagcccc tgttgggcca ccccatgccc ggatctccca gcatggagac 720
ccattgctgt ccaacacctt cactgagacc aacaaccact ggccccaggg acccactggg 780
cctccaggcc ctccagggcc catgggtccc cctgggcctc ctggccccac aggtgtccct 840
gggagtcctg gtcacatagg acccccaggc cccactggac ccaaaggaat ctctggccac 900
ccaggagaga agggcgagag aggactgcgt ggggagcctg gcccccaagg ctctgctggg 960
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ggacccccag cytcttcggg gcaagagggg cggacatgca accaaactac cggatcgtgg 1200
gccccaagaa cccgggacga agagaagctn annggn 1236

<210> 27
<211> 832
<212> DNA
<213> Homo sapiens

<400> 27
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agaggggcgg acatgcaacc aactaccgga tcgtggcccc caggagccgg gacgagagag 180
gctgagggtg gtggcggccc ctgaggcaga ccaggccagg cttcccctcc tacctggact 240
cggccagctg cctccaggga ccgcccgtcc atatttatta atgtcctcag ggtcccttct 300
gccatctagg ccttaggggt aagcaggtct cagtcctggc accatgcaca tgtctgaggc 360
tgagcaaggg ctgagaggag aggcttgggc ctcagtttcc ctctgtgaag tggggggagg 420
caggccttca aggagggata gaggtacaag gcttcgtctc atctgctgtc tgagcatcca 480
ggcccaaagg cactgaggga gtcaggagct ggggctcggc acatgcagag atgacagggc 540
agggggcagt cttcctcccc ctccccgacc aaacctcggg gagccctcct gtgcccctcc 600
ctccttgttg tccagtgctg ggttccccac cccgaggtca ggctgcccaa tcctctgact 660
ggatcaccgg gggcttcttg cctcagttct tccctctgag cccccaggcc ctcccgcatc 720
tcaggttggg gatggggaca tggagaggaa ggggccgcct actcctgcaa atgcttgtga 780
cagatgccag gaggtagatg ctgtctctta tacacatctc aaccatcatc ga 832

<210> 28
<211> 1967
<212> DNA
<213> Homo sapiens

<400> 28
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cgttctccgg acgcaggaac tggtgctcct atgtggtgac ccgcaccatc tcatgccatg 180
tgcagaatgg cacctacctt cagcgagtgc tgcagaactg cccctggccc atgagctgtc 240
cggggagcag ctacagaact gtggtgagac ccacatacaa ggtgatgtac aagatagtga 300
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cttcctctgc ctccttggag cccatgtggt cgggcagtac catgcggcgg atggcgcttc 420
ggcccacagc cttctcaggt tgtctcaact gcagcaaagt gtcagagctg acagagcggc 480
tgaaggtgct ggaggccaag atgaccatgc tgactgtcat agagcagcca gtaccttcaa 540
caccagctac ccctgaggac cctgccccgc tctggggtcc ccctcctgcc cagggcagcc 600
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ccaagggaga tgccggcagt cggggcccaa tggggatgag aggcccacca ggtccacagg 720

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gccccccagg gagccctggc cgggctggag ctgtgggcac ccctggagag aggggacctc     780
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actggcccca gggacccact gggcctccag gccctccagg gcccatgggt ccccctgggc     960
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cagcctcctt cggggcaaga ggggcggaca tgcaaccaac taccggatcg tggcccccag    1260
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ccaggccctc ccgcatctca ggttggggat ggggacatgg agaggaaggg gccgcctact    1860
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acctgattcc ccgcaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa                  1967
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<210> 29
<211> 1967
<212> DNA
<213> Homo sapiens

<400> 29

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cgttctccgg acgcaggaac tggtgctcct atgtggtgac ccgcaccatc tcatgccatg     180
tgcagaatgg cacctacctt cagcgagtgc tgcagaactg cccctggccc atgagctgtc     240
cggggagcag ctacagaact gtggtgagac ccacatacaa ggtgatgtac aagatagtga     300
ccgcccgtga gtggaggtgc tgccctgggc actcaggagt gagctgcgag gaagttgcag     360
cttcctctgc ctccttggag cccatgtggt cgggcagtac catgcggcgg atggcgcttc     420
ggcccacagc cttctcaggt tgtctcaact gcagcaaagt gtcagagctg acagagcggc     480
tgaaggtgct ggaggccaag atgaccatgc tgactgtcat agagcagcca gtacctccaa     540
caccagctac ccctgaggac cctgccccgc tctggggtcc ccctcctgcc cagggcagcc     600
ccggagatgg aggcctccag gaccaagtcg gtgcttgggg gcttcccggg cccaccggcc     660
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gccccccagg gagccctggc cgggctggag ctgtgggcac ccctggagag aggggacctc     780
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actggcccca gggacccact gggcctccag gccctccagg gcccatgggt ccccctgggc     960
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cctgcaaatg cttgtgacag atgccaggag gtagatgtgt gctggccaat aaaggcccct    1920
acctgattcc ccgcaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa                  1967
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<210> 30
<211> 2006
<212> DNA
<213> Homo sapiens

<400> 30
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cgttctccgg acgcaggaac tggtgctcct atgtggtgac ccgcaccatc tcatgccatg     180
tgcagaatgg cacctacctt cagcgagtgc tgcagaactg cccctggccc atgagctgtc     240
cggggagcag ctacagaact gtggtgagac ccacatacaa ggtgatgtac aagatagtga     300
ccgcccgtga gtggaggtgc tgccctgggc actcaggagt gagctgcgag gaagttgcag     360
cttcctctgc ctccttggag cccatgtggt cgggcagtac catgcggcgg atggcgcttc     420
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tgaaggtgct ggaggccaag atgaccatgc tgactgtcat agagcagcca gtacctccaa     540
caccagctac ccctgaggac cctgccccgc tctggggtcc ccctcctgcc cagggcagcc     600
ccggagatgg aggcctccag gaccaagtcg gtgcttgggg gcttcccggg cccaccggcc     660
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gcccccccagg gagccctggc cgggctggag ctgtgggcac ccctggagag aggggacctc     780
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caggccctcc cgcatctcag gttggggatg ggacatggga gaggaagggg ccgcctactc    1860
ctgcaaatgc ttgtgacaga tgccaggagg tagatgtgtg ctggccaata aaggccccta    1920
cctgattccc cgcaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa    1980
aaaaaaaaaa aaaaaaaaaa aaaaaa                                         2006
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<210> 31
<211> 897
<212> DNA
<213> Homo sapiens

<400> 31
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cggtccccca ggacctccag gtgcagaagt gaccgcggag actctgcttc acgagtttca     180
ggagctgctg aaagaggcca cggagcgccg gttctcaggg cttctggacc cgctgctgcc     240
ccaggggggcg ggcctgcggc tggtgggcga ggcctttcac tgccggctgc agggtccccg     300
ccgggtggac aagcggacgc tggtggagct gcatggtttc caggctcctg ctgcccaagg     360
tgccttcctg cgaggctccg gtctgagcct ggcctcgggt cggttcacgg cccccgtgtc     420
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gtgagggcgc ccaggggggc tggcgaggag ctgccgccgg atcccgggga ccctcctact     780
gatgcccgtg gtcaccacaa taaagagccc tccaccctca aaaaaaaaaa aaaaaaaaaa     840
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa        897
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<210> 32
<211> 990
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (751)..(751)

<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (879)..(879)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (888)..(888)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (897)..(897)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (899)..(899)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (901)..(901)
<223> n equals a,t,g, or c

<400> 32
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atggagaggg ggttcagcga gcctagagag ggcagactat cagggtgccg gcggtgagaa 120
tccagggaga ggagcggaaa cagaagaggg gcagaagacc ggggcacttg tgggttgcag 180
agcccctcag ccatgttggg agccaagcca cactggctac caggtcccct acacagtccc 240
gggctgccct tggttctggt gcttctggcc ctgggggccg ggtgggccca ggaggggtca 300
gagcccgtcc tgctggaggg ggagtgcctg gtggtctgtg agcctggccg agctgctgca 360
ggggggcccg ggggagcagc cctgggagag gcaccccctg ggcgagtggc atttgytgcg 420
gtccgaagcc accaccatga gccagcaggg gaaaccggca atggcaccag tggggccatc 480
tacttcgacc aggtcctggt gaacgagggc ggtggctttg accgggcctc tggctccttc 540
gtagcccctg tccggggtgt ctacagcttc cggttccatg tggtgaaggt gtacaaccgc 600
caaactgtcc aggtgagcct gatgctgaac acgtggcctg tcatctcagc ctttgccaat 660
gatcctgacg tgacccggga ggcagccacc agctctgtgc tactgccctt ggaccctggg 720
gaccgagtgt ctctgcgcct gcgtcggggg naatctactg ggtggttgga aatactcaag 780
tttctctggc ttcctcatct tccctctctg aaggacccaa gtctttcaag cacaagaatc 840
cagcccctga caactttctt ctgccctctc ttgccccana aacagcanaa gcagganana 900
nactccctct ggctcctatc ccacctcttt gcatgggaac ctgtgccaaa cacccaagtt 960
taagaaaaaa ataaaactgt ggcatctcca 990

<210> 33
<211> 1384
<212> DNA
<213> Homo sapiens

<400> 33
tcgagttttt tttttttttt tttgaccacc attctctagt tgttttattg atagattcat 60
ccaggctggg ccaatgggac agcgggataa gaaagagaga gggagggttt agcatactgg 120
caggagaggg tctgaaggaa tgaatcatgg aatcccaggt aataggaagc ctaaggagga 180
gaataagaca gcacagatca ggagaaagag agatagtggg gatatgctgg aacaggtaca 240
gtgaarataa ctcagtgaga gagctgggag gaaggaggca gcagtcagag tktggaggga 300
ctaaagttca aacttcaaag gtggacagtt tcaggaggtg gccaagcaag argatgcatg 360
gttatcsatg ttttccatgg tccacttcca gctctgtata cctgccwcag ytytrytytt 420
ytcttaaact tgggtgtttg gcacaggktc ccatgcaaag argtgggata ggarccagag 480
ggagtctctc tcctgcctct gctgtttctg gggcaagaga gggcagaaga aagttgtcag 540
gggctggatt cttgtgcttg aaaracttgg gtcctcagag agggaagatg aggaagccag 600
agaaacttga gtatttccaa ccacccagta gattccccccg acgcaggcgc agagacactc 660
ggtccccagg gtccaagggc agtagcacag agctggtggc tgcctcccgg gtcacgtcag 720
gatcattggc aaaggctgag atgacaggcc acgtgttcag catcaggctc acctggacag 780
tttggcggtt gtacaccttc accacatgga accggaagct gtagacaccc cggacagggg 840
ctacgaagga gccagaggcc cggtcaaagc caccgccctc gttcaccagg acctggtcga 900

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agtagatggc cccamtggtg ccattgccgg tttcccctgc tggctcatgg tgktggcttc     960
ggaccgcagc aaatgccact cgcccagggg gtgcctctcc cagggctgct cccccgggcc    1020
cccctgcagc agctcggcca ggctcacaga ccaccaggca ctccccctcc agcaggacgg    1080
gctctgaccc ctcctgggcc cacccggccc ccagggccag aagcaccaga accaagggca    1140
gcccgggact gtgtagggga cctggtagcc agtgtggctt ggctcccaac atggctgagg    1200
ggctctgcaa cccacaagtg ccccggtctt ctgcccctct tctgtttccg ctcctctccc    1260
tggattctca ccgccggcac cctgatagtc tgccctctct aggctcgctg aaccccctct    1320
ccatacctgt gtcccagctc tgtcctgcct cccactctta ctcctgctgt cactgcagtt    1380
cccc                                                                 1384
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<210> 34
<211> 809
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (307)..(307)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (751)..(751)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (756)..(756)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (804)..(804)
<223> n equals a,t,g, or c

<400> 34

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cgcctgctgc cccgtgcggg cgcagaacga cacggagccc atcgtgctgg agggcaagtg      60
cctggtggtg tgcgactcca gcccgtcggc ggacggcgcc gtcacctcct ccctaggcat     120
ctccgtgcgc tccggcagcg ccaaggtggc cttctccgcc acgcggagca ccaaccacga     180
gccgtccgag atgagcaacc gcaccatgac catctatttc gaccaggtat tagtaaatat     240
tggcaaccac tttgatcttg cttccagtat atttgtagca ccgagaaaag ggatttatag     300
cttcagnttc cacgtggtca aagtgtataa cagacaaacc atccaggtca gtttaatgca     360
gaatggctac ccagtgatct cggcctttgc aggagaccag gatgtcacca gagaagctgc     420
tagcaatggc gtgctgctgc tcatggaaag ggaagacaaa gtgcatctca aacttgagag     480
aggcaacctc atgggggggct ggaaatactc cacattctcg ggcttcttgg tgtttcctct     540
ataaacacag agccccctag atggtggggg aatggcaaac tggacccagg actccgccct     600
ttaaaacacc ctggaactta ctggaattgg acaccttgtt tccaacctcc gttcagactg     660
tttgcagtag gaaggaatga tttcctttgg aaacctccag tacttttgtt ttgtttttttg     720
ggattattga catttcctcg ggaaccgggc ntttanttag tttttagatg gacaaggtct     780
ttaagggaga attgaatttt tcgntttga                                       809
```

<210> 35
<211> 1215
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1212)..(1212)
<223> n equals a,t,g, or c

<400> 35

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gcggccgcag ctccagctcc cggtgtccgg gactcgggtc tcccgccagg gggcgccact      60
ccccgcgctt tgcagccctg agcgggggag gggcccaggc ggcgggagcc cccttggcca     120
gccccccaga tctgccctgc gggaaggggt ggaggaggta cccgtgcggg aggaggcgct     180
ggccgaagct caggcagggg cggggagggg tacggtgacc ttagagtcgc cgccccgctg     240
cgggctgagc cgccgctact ctcamcctgc cgccccgctt accccgcagg actgccggga     300
```

```
cctcgagggg accccgggcc gcgaggagag gcgggacccg cggggcccac cgggcctgcc     360
ggggagtgct cggtgcctcc gcgatccgcc ttcagcgcca agcgctccga gagccgggtg     420
cctccgccgt ctgacgcacc cttgcccttc gaccgcgtgc tggtgaacga gcagggacat     480
tacgacgccg tcaccggcaa gttcacctgc caggtgcctg ggtctacta  cttcgccgtc     540
catgccaccg tctaccgggc cagcctgcag tttgatctgg tgaagaatgg cgaatccatt     600
gcctctttct tccagttttt cggggggtgg cccaagccag cctcgctctc ggkgggggcc     660
atggtgaggc tggagcctga ggaccaagtg tgggtgcagg tgggtgtggg tgactacatt     720
ggcatctatg ccagcatcaa gacagacagc accttctccg gatttctggt gtactccgac     780
tggcacagct ccccagtctt tgcttagtgc ccactgcaaa gtgagctcat gctctcactc     840
ctagaaggag ggtgtgaggc tgacaaccag gtcatccagg agggctggcc cccctggaat     900
attgtgaatg actagggagg tggggtagag cactctccgt cctgctgctg gcaaggaatg     960
ggaacagtgg ctgtctgcga tcaggtctgg cagcatgggg cagtggctgg atttctgccc    1020
aagaccagag gagtgtgctg tgctggcaag tgtaagtccc ccagttgctc tggtccagga    1080
gcccacggtg ggtgctctc  ttcctggtcc tctgcttctc tggatcctcc ccaccccctc    1140
ctgctcctgg ggccggccct tttctcagag atcactcaat aaacctaaga accctcaaaa    1200
aaaaaaaaaa anggg                                                     1215
```

<210> 36
<211> 1311
<212> DNA
<213> Homo sapiens

<400> 36

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ggtcgaccca cgcgtccgca ctcagacacc gtgtcctctt gcctgggaga ggggaagcag      60
atctgaggac atctctgtgc caggccagaa accgcccacc tgcagttcct tctccgggat     120
ggacgtgggg cccagctccc tgccccacct tgggctgaag ctgctgctgc tcctgctgct     180
gctgcccctc aggggccaag ccaacacagg ctgctacggg atcccaggga tgcccggcct     240
gcccggggca ccagggaagg atgggtacga cggactgccg ggcccaagg  gggagccagg     300
aatcccagcc attcccggga tccgaggacc caaagggcag aagggagaac ccggcttacc     360
cggccatcct gggaaaaatg gccccatggg acccccctggg atgccagggg tgcccggccc     420
catgggcatc cctggagagc caggtgagga gggcagatac aagcagaaat tccagtcagt     480
gttcacggtc actcggcaga cccaccagcc ccctgcaccc aacagcctga tcagattcaa     540
cgcggtcctc accaacccgc agggagatta tgacacgagc actggcaagt tcacctgcaa     600
agtccccggc ctctactact ttgtctacca cgcgtcgcat acagccaacc tgtgcgtgct     660
gctgtaccgc agcggcgtca aagtggtcac cttctgtggc cacacgtcca aaaccaatca     720
ggtcaactcg ggcggtgtgc tgctgaggtt gcaggtgggc gaggaggtgt ggctggctgt     780
caatgactac tacgacatgg tgggcatcca gggctctgac agcgtcttct ccggcttcct     840
gctcttcccc gactagggcg ggcagatgcg ctcgagcccc acgggccttc cacctccctc     900
agcttcctgc atggacccac cttactggcc agtctgcatc cttgcctaga ccattctccc     960
caccagatgg acttctcctc cagggagccc accctgaccc acccccactg cacccccctcc    1020
ccatgggttc tctccttcct ctgaacttct ttaggagtca ctgcttgtgt ggttcctggg    1080
acacttaacc aatgccttct ggtactgcca ttcttttttt ttttttttttc aagtattgga    1140
aggggtgggg agatatataa ataaatcatg aaatcaatac awaaaaaaaa aaaaaaaaaa    1200
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa    1260
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a             1311
```

<210> 37
<211> 350
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (4)..(4)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (7)..(7)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (9)..(9)
<223> n equals a,t,g, or c

<400> 37

gggnatnang cttcctgctc ttccccgact agggcgggca gatgcgctcg agacccacgg 60
gccttccacc tccctcagct tcctgcatgg acccacctta ctggccagtc tgcatccttg 120
cctagaccat tctcccctcc agggagccca ccctgaccca cccccactgc accccctccc 180
catgggttct ctccttcctc tgaacttctt taggagtcac tgcttgtgtg gttcctggga 240
cacttaacca atgccttctg gtactgccat tctttttttt ttttttttcaa gtattggaag 300
gggtggggag atatataaat aaatcatgaa atcaaaaaaa aaaaaaaaag 350

<210> 38
<211> 622
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (316)..(316)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (511)..(511)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (525)..(525)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (578)..(578)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (582)..(582)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (599)..(599)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (614)..(614)
<223> n equals a,t,g, or c

<400> 38
ggggagcaga tctgaggaca tctctgtgcc aggccagaaa ccgcccacct gcagttcctt 60
ctccgggatg gacgtggggc ccagctccct gccccacctt gggctgaagc tgctgctgct 120
cctgctgctg ctgcccctca ggggccaagc caacacaggc tgctacggga tcccagggat 180
gcccggcctg ccyggggcac cagggaagga tgggtacgac ggactgccgg ggcccaaggg 240
ggagccagga atccagccat tccgggatcc gaggacccaa arggcagaag ggagaacccg 300
gcttacccgg ccatcntggg aaaawtggyc catggkaccc cctgggatgc caggggtgcc 360
ggcccatggg catccctgga gagcaggtga gragggcaga tacaagcaga aattccagtc 420
aktgtcacgg cactcggaga ccacagcccc tgacccaaca gctgatagat caacgcggtc 480
taacaaccga aggagatata cacgacactg naagtcactg aaagnccggc ttacacttgc 540
tacacgcgtg ataagcaact ggctgtgtga cgaacggnta angggcactt tgggcaacnc 600
aaacataggc aatngcgggg ct 622

<210> 39
<211> 1333
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature

<222> (485)..(486)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (493)..(493)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (496)..(496)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (587)..(587)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (633)..(633)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1330)..(1330)
<223> n equals a,t,g, or c

<400> 39
agctggtacc aaagcaagtt tttcactgag ctctcatgaa agatcctcag tctcttgtgg 60
atttagaatc ctgcagcagc ccaccatcta agagcaagar ccaaagatgt ttgtcttgct 120
ctatgttaca agttttgcca tttgtgccag tggacaaccc cggggtaatc agttgaaagg 180
agagaactac tcccccaggt atatctgcag cattcctggc ttgcctggac ctccagggcc 240
ccctggagca aatggttccc ctgggcccca tggtcgcatc ggccttccag gaagagatgg 300
tagagacggc aggaaaggag agaaaggtga aaagggaact gcaggtttga gaggtaagac 360
tggaccgcta ggtcttgccg gtgagaaagg ggaccaagga gagactggga agaaaggacc 420
cataggacca gagggagaga aaggagaagt aggtccaatt ggtcctcctg gaccaaaggg 480
agacnnatga tanctntggg acccggggct gcctggagtt tgcagatgtg gaagcatcgt 540
gctcaaatcc gccttttctg ttggcatcac aaccagctac ccagaanaaa gactacctat 600
tatatttaac aaggtcctcc ttccacgagg ganagcacta caaccctgcc acaggggaag 660
ttcatctgtg ctttcccagg ggatctatta cttttcttat gatatcacat tggctaataa 720
gcatctggca atcggactgg tacacaatgg gcaataccgg ataaagacct tcgacgccaa 780
cacaggaaac catgatgtgg cttcggggtc cacagtcatc tatctgcagc cagaagatga 840
agtctggctg gagattttct tcacagacca gaatggcctc ttctcagacc caggttgggc 900
agacagctta ttctccgggt ttctcttata cgttgacaca gattacctag attccatatc 960
agaagatgat gaattgtgat caggaccaag atccctgtgg taaacactct gattgaatct 1020
ggggttccag aaggtggaac aagcaggaat gggatccaaa gagactccca ctcagattct 1080
aaagcattta aagacaattc tagcagaatt tatcaaaaca agatgaaaca cagaaaagtt 1140
gaaaccacaa caaaatgaat tctattaaag aatagcccca gatataaatt ctcttgaaag 1200
caatgttcat aaatatttaa gcaaattaaa gacaatgtta acaaattttc tattaaatgc 1260
cctgagtgat aaaaccagtt ggcaataata ttgccttatt aaatcttcaa aaaataaaaa 1320
aaattaaaan aaa 1333

<210> 40
<211> 1211
<212> DNA
<213> Homo sapiens

<400> 40
tcgagttttt tttttttttt tttgatgaat aaaaaggttt ggatttaatg aaggggaaaa 60
aaagaggcrg aggaggtgag cctgaggcta gaaccgctca ctcgaccccc cacccccagc 120
ctacagttgt ggggtcttgc tctgtaagcc caagtccaga agcttgttcc ctgcctggag 180
gaccgccgtg gcatgtctat acctcgttgg ggtcatcctg gtcggcatag attaggaagc 240
ccgtaaagag gctgtctgtc cagtaagggt catagaagag cccgttctgc tctgagtaga 300
agatctgcag ccaacttcg tcaccctgct tgagagccag gatggtggag cctgaggcca 360
catcgtggtt gccggtgttg gcatcaaagg tccggatgcg gtactggccg ttgtgcacca 420
ggccgatggc caggtgcttg ttggccagcg tgatgtcgta ggtgaagtag tagatcccag 480

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gcacgccgca gacgaacttg ccgctggaag cattgtagtg gccaccctcg ttcatcagaa    540
tcttgtcaaa cttgatgggc agccgctccc gtgggtagct cttggtcact gccaccgaga    600
aagctgactt ggtatggcca ctgccacagc tgcaggggcc tgggaggcct ggctccccct    660
tcttgccctt gggccccttc ttgcctggtg tgccatgctt cccgggggta ccgttgaccc    720
ccttggggcc acgggggcca gcccgcccaa tggccccggc tttgcccttt ggtcctggct    780
ttccccggtt acctgtccgg ccaggtggac cttcctctcc gctgtccccc cggtcgccgt    840
cgtgtccatc ttggccgtct ttgccaggaa agcccattcg tcccatcatt cctgagggcc    900
ctggggctcc tgggggccg ggtgggccct gggggccagg caggctgcag accagttgag     960
gggagccttt ccggaagtcc ctgcgagcaa aggcgccaag cagtgggtca gcagcacagg   1020
ggagggcaca ggccaggagc acccagggga tcatggtggt taccctcgcg gctgcccgcc   1080
acgtccaggg gcgtccggag caaagaagct cctcgtgccg aattcctgca gcccggggga   1140
tccactagtt ctagagcggc cgccaccgcg gtggagctcc agcttttgtt cccwttagga   1200
ggaagattcc c                                                        1211
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<210> 41
<211> 616
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (262)..(262)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (536)..(536)
<223> n equals a,t,g, or c

<400> 41

```
ggcacagcgc acgcaacttg gtgggctcgg acgctggccc cgggcgcggc accaaccact     60
cgccttcgac accgagttcg tcaacattgg cggcgacttc gacgcgrcgg ccggcgtgtt    120
ccgctgccgt ctgcccggcg cctacttctt ctccttcacg ctgggcaagc tgccgcgtaa    180
gacgctgtcg gttaagctga tgaagaaccg cgacgaggtg caggccatga tttacgacga    240
cggcgcgtcg cggcgccgcg angatgcaga gccagagcgt gatgctggcc ctgcggcgcg    300
gcgacgyctc tggctgctca gccacgacca cgacggctac ggcgcctaca gcaaccacgg    360
caagtacatc accttctccg gcttcctggt gtaccccgac ctcgcccccg ccgcccgccg    420
ggcctcgggg cctcggagct actgtgagcc ccgggccaga gaagagcccg ggagggccag    480
gggcgtgcat gccaggccgg gcccgaggct cgaaagtccc gcgcgagcgc cacggnctcc    540
gggcgcgcct ggactctgcc aataaagcgg aaagcgggca cggcaggccc ggmagcccag    600
gmaaaaaaaa aaaaaa                                                    616
```

<210> 42
<211> 1161
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1113)..(1113)
<223> n equals a,t,g, or c

<400> 42

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gccagcctgc tggtccatgg gaggggaccg tcaggggaaa gcccttcccg cctctgggga     60
agggaacttc cgcttcggac cgagggcagt aggctctcgg ctcctggtcc cactgctgct    120
cagcccagtg gcctcacagg acaccagctt cccaggaggc gtctgacaca gtatgatgat    180
gaagatccca tggggcagca tcccagtact gatgttgctc ctgctcctgg gcctaatcga    240
tatctcccag gcccagctca gctgcaccgg gcccccagcc atccctggca tcccgggtat    300
ccctgggaca cctggccccg atggccaacc tgggacccca gggataaaag gagagaaagg    360
gcttccaggg ctggctggag accatggtga gttcggagag aagggagacc cagggattcc    420
tgggaatcca ggaaaagtcg gccccaaggg ccccatgggc cctaaaggtg gcccaggggc    480
ccctggagcc ccaggcccca aaggtgaatc gggagactac aaggccaccc agaaaatcgc    540
cttctctgcc acaagaacca tcaacgtccc cctgcgccgg gaccagacca tccgcttcga    600
ccacgtgatc accaacatga acaacaatta tgagccccgc agtggcaagt tcacctgcaa    660
ggtgcccggt ctctactact tcacctacca cgccagctct cgagggaacc tgtgcgtgaa    720
cctcatgcgt ggccgggagc gtgcacagaa ggtggtcacc ttctgtgact atgcctacaa    780
caccttccag gtcaccaccg gtggcatggt cctcaagctg gagcaggggg agaacgtctt    840
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cctgcaggcc accgacaaga actcactact gggcatggag ggtgccaaca gcatcttttc     900
cgggttcctg ctctttccag atatggaggc ctgacctgtg ggctgcttca catccacccc     960
ggctccccct gccagcaacg ctcactctac ccccaacacc acccccttgcc cagccaatgc  1020
acacagtagg gcttggtgaa tgctgctgag tgaatgagta aataaactct tcaaggccaa   1080
aaaaaaaaaa aaaaagcact taagtattca tcnaacaatc acccagtagc ggtgatccag   1140
actgaaaaga tgcgagacgc c                                             1161
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<210> 43
<211> 687
<212> DNA
<213> Homo sapiens

<400> 43

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ccggggcccc cccccgagtt tttttttttt tttttggcct tgaaragttt atttactcat      60
tcactcagca gcattcacca agccctactg kgtgcattgg ctgggcaagg ggkggkgttg     120
ggggtagagk gagcgttgct ggcagggggga gccggggtgg atgtgaagca gcccacaggt    180
caggcctcca tatctggaaa gagcaggaac ccggaaaaga tgctgttggc accctccatg     240
cccagtagtg agttcttgtc ggtggcctgc aggaagacgt tctccccctg ctccagcttg     300
aggaccatgc caccggtggt gacctggaag gtgttgtagg catagtcaca gaaggtgacc     360
accttctgtg cacgctcccg gccacgcatg aggttcacgc acaggttccc tcgagagctg     420
gcgtggtagg tgaagtakta ragaccgggc accttgcagg tgaacttgcc actgcggggc     480
tcataattgt tgktcatgtt ggkgatcacg tggtcsaagc ggatggtctg gtcccsgcgc     540
agggggacgt tgatggktct tgtggcarar aaaggcattt tctgggkggc ctgagtctcc     600
cgattcacct ttgggctggg ggcttcgggc ccctgggcaa ccttaggccc atgggggcct     660
tggggccgcc ttttcctgat tccagga                                         687
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<210> 44
<211> 1194
<212> DNA
<213> Homo sapiens

<400> 44

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ggcctcacag gacaccagct tcccaggagg cgtctgacac agtatgatga tgaagatccc     180
atggggcagc atcccagtac tgatgttgct cctgctcctg ggcctaatcg atatctccca     240
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cacaagaacc atcaacgtcc ccctgcgccg ggaccagacc atccgcttcg accacgtgat     600
caccaacatg aacaacaatt atgagccccg cagtggcaag ttcacctgca aggtgcccgg     660
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gtctaattca actctgtgtc ccagcacctg gcacaccaga agtgccatgc tcagaaatgt   1140
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<210> 45
<211> 1792
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (19)..(19)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (132)..(132)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (185)..(185)
<223> n equals a,t,g, or c

<400> 45
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gaagacccgg gnccgatcca gcytccggac tctagcttag cccgcggacg gataccawtt 180
tcacncagga accagctatg accactaggc ttttgcaaaa agctatttag gtgacactat 240
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gcctgggact taacctgctc aggcgggcct tcgcccagct gcaaataggg atgcgttaga 1560
gactgttccc aaagcttgtt gggctcctta aatggcatgt acaatttaag tgcaaagaca 1620
gggagtgtca ataaagatgg aaagccattt ccagttaaaa aaaaaaaaaa aaaaaaaaaa 1680
aaaaaaaaaa aaaaaagggc ggccgctcta gaggatccct cgagggggccc aagcttacgc 1740
gtgcatgcga cgtcatagct ctctccctat agtagtcgta ttataagtag ct 1792

<210> 46
<211> 1412
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1363)..(1363)
<223> n equals a,t,g, or c

<400> 46
ccacgcgtcc ggtcctgccc cagcggcccc ccgaggagag gccgccccag ccgccaggct 60
ccaccggggt catcgcggag acgggccagg ccgggccccc cgcaggcgca ggcgtgtctg 120
ggcggggtct gccgcggggc gtggacggcc agaccgggag cggcaccgtc cccggcgcag 180
aaggcttcgc gggcgcacca ggatacccga agtcacctcc tgtagcttcc ccaggagctc 240
cggtgccttc tctggtgtct ttttctgcgg ggctcaccca gaagcctttc cccagtgatg 300
ggggcgttgt cctctttaac aaagtgctgg tgaacgacgg ggatgtttac aaccccagca 360
ccggggtctt cacggctcct tatgatgggc gctacctgat cacggccacc ctcacccccg 420
agagagacgc ctacgtggaa gcagtgctgt cggtctccaa cgccagcgtg gcccagctgc 480
ataccgctgg gtacaggaga gagttcctgg aataccaccg ccctccagga gctttgcata 540
cctgcggggg cccgggggca ttccacctca tcgtgcacct gaaggcggga gatgcagtca 600
acgtcgtggt gactgggggc aagctggctc acacagactt tgatgaaatg tactccacat 660
ttagtggggt ttttcttatat cctttccttt cccacctcta aggtggctgg ggagatgtca 720
ggggaaagac agatagttgt aaaaactcta aagctttaat atattcggtt tgtatgtaat 780
ggaagcacgg ggctagagtt tccacatagg ccccaacata aaggccttcc ctcgctgttg 840
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tttaagtgca aagacaggga gtgtcaataa agatggaaag ccntttccag ttaaaaaaaa 1380
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa 1412

<210> 47
<211> 646
<212> DNA
<213> Homo sapiens

<400> 47
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gtttcaccta tggaatgaga aagttgggga agaagtcatc tagcgtcttg ctactcaaag 120
tgtggtccat ggaccagcag catcagcatc acctgggatc ttcttggaag aaatgtagaa 180
actcaggcct cacccccagaa tctgcctttt tataagaccc ccagaagctg ttgtgaaggc 240
agagcagcat ctgctgaaga gacagaaacc agccccagag gtgtcacagg aagtcaccag 300
caaggacatt ggtctttgat ttgattcagc agtcctgtca agtataaatg tgatggctgt 360
gctgcctggc cctctgcagc tgctgggagt gctgcttacc atttccctga gttccatcag 420
gctcattcag gctggtgcct actatgggat caagccgctg ccacctcaaa ttcctcctca 480
gatgccacca caaattccac aataccagcc cctgggtcag caagtacctc acatgccttt 540
ggccaaagat ggccttgcca tgggcaagga gatgccccac ttgcagtatg gcaaagagta 600
tccacaccta ccccaatata tgaaggaaat tcaaccggcg gtcgac 646

<210> 48
<211> 2536
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2)..(3)
<223> n equals a,t,g, or c

<400> 48
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cggcacctcg cagggctggc ggtgggccgc aggccccctc aggaatgctg ctctccagag 120
ctgggccggc gactggcaga gctggagcgc aggctggatg tcgtggccgg ctcagtgaca 180
gtgctgagtg ggcggcgagg cacagagctg ggaggagccg cggggcaggg aggccacccc 240
ccaggctaca ccagcttggc ctcccgcctg tctcgcctgg aggaccgctt caactccacc 300
ctgggccctt cggaggagca ggaggagagc tggcctgggg ctcctggggg gctgagccac 360
tggctgcctg ctgcccgggg ccgactagag cagttggggg ggctgctggc caatgtgagc 420
gggkagctgg gggggcggtt ggatctgttg gaggagcagg tggcaggggc catgcaggca 480
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agtgccttgg agcgcagggt gctggacagt gaggggcagc tgcggctggt gggctccggc 600
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caggccgggg acacggtctg cgtcgacctg gtcatggggc agctggcgca ctcggaggag   2040
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actggggtcc cgcccgacgt gtctacgtcg gctgaagaga cagcgggggc ggcgggctcc   2160
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cggcaccgcg cccagagcgg cctctcccca cgcccggggc gcgccggctc agggaggctc   2280
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cctgggctcc aggctccccc gcgcgggcgc cgcccaccgc catactaaac gatcgaggaa   2460
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aaaaaaaggc ggccgc                                                   2536
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<210> 49
<211> 1530
<212> DNA
<213> Homo sapiens

<400> 49

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ggagtgaacc cagctgaacc tgggccgcag cagccccgga ggctggaggc gctgcagtcg    180
ggaaacacca ggaggatgga gcccttttcc ctgtaagcag gaggccagga tcctgattcc    240
tgagccggct tcccacggac cccaggcccc ggcagggtcc tggcgggagg aagaacccac    300
ggattcagag tctgtcatct gaaccatgag gatctggtgg cttctgcttg ccattgaaat    360
ctgcacaggg aacataaact cacaggacac ctgcaggcaa gggcaccctg gaatccctgg    420
gaaccccggt cacaatggtc tgcctggaag agatggacga gacggagcga agggtgacaa    480
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ctcaagagga tccccaggaa aacatggccc caaggggctt gcagggccca tgggagagaa    660
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aacttattca gatggtttta ctttattaat tcctccaatt attacaataa tcataaaaag   1440
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<210> 50
<211> 229
<212> PRT
<213> Homo sapiens

<400> 50

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Met Asp Leu Leu Gln Phe Leu Ala Phe Leu Phe Val Leu Leu Leu Ser
1               5                   10                  15

Gly Met Gly Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser Leu
            20                  25                  30

Glu Ile Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu Leu
        35                  40                  45

Ala Leu Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr Lys
    50                  55                  60

Ile Leu Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp Ser
65                  70                  75                  80
```

Arg Thr Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Cys Pro
85 90 95

Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn Thr
100 105 110

Ala Phe Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His Tyr
115 120 125

Tyr Phe Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly Ile
130 135 140

Ser Phe Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser Pro
145 150 155 160

Ile Leu Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp Ser
165 170 175

Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro Ser
180 185 190

Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg Lys
195 200 205

Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser Arg
210 215 220

Ser Gln Ser Glu Leu
225

<210> 51
<211> 421
<212> PRT
<213> Homo sapiens

<400> 51
Met Gly Gly Pro Arg Ala Trp Ala Leu Leu Cys Leu Gly Leu Leu Leu
1 5 10 15

Pro Gly Gly Gly Ala Ala Trp Ser Ile Gly Ala Ala Pro Phe Ser Gly
20 25 30

Arg Arg Asn Trp Cys Ser Tyr Val Val Thr Arg Thr Ile Ser Cys His
35 40 45

Val Gln Asn Gly Thr Tyr Leu Gln Arg Val Leu Gln Asn Cys Pro Trp
50 55 60

Pro Met Ser Cys Pro Gly Ser Ser Tyr Arg Thr Val Val Arg Pro Thr
65 70 75 80

Tyr Lys Val Met Tyr Lys Ile Val Thr Ala Arg Glu Trp Arg Cys Cys
85 90 95

Pro Gly His Ser Gly Val Ser Cys Glu Glu Val Ala Ala Ser Ser Ala
100 105 110

Ser Leu Glu Pro Met Trp Ser Gly Ser Thr Met Arg Arg Met Ala Leu
115 120 125

Arg Pro Thr Ala Phe Ser Gly Cys Leu Asn Cys Ser Lys Val Ser Glu
130 135 140

Leu Thr Glu Arg Leu Lys Val Leu Glu Ala Lys Met Thr Met Leu Thr
145 150 155 160

Val Ile Glu Gln Pro Val Pro Pro Thr Pro Ala Thr Pro Glu Asp Pro
165 170 175

Ala Pro Leu Trp Gly Pro Pro Pro Ala Gln Gly Ser Pro Gly Asp Gly
180 185 190

Gly Leu Gln Asp Gln Val Gly Ala Trp Gly Leu Pro Gly Pro Thr Gly
195 200 205

Pro Lys Gly Asp Ala Gly Ser Arg Gly Pro Met Gly Met Arg Gly Pro
210 215 220

Pro Gly Pro Gln Gly Pro Pro Gly Ser Pro Gly Arg Ala Gly Ala Val
225 230 235 240

Gly Thr Pro Gly Glu Arg Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly
245 250 255

Pro Pro Gly Pro Pro Ala Pro Val Gly Pro Pro His Ala Arg Ile Ser
260 265 270

Gln His Gly Asp Pro Leu Leu Ser Asn Thr Phe Thr Glu Thr Asn Asn
275 280 285

His Trp Pro Gln Gly Pro Thr Gly Pro Pro Gly Pro Pro Gly Pro Met
290 295 300

Gly Pro Pro Gly Pro Pro Gly Pro Thr Gly Val Pro Gly Ser Pro Gly
305 310 315 320

His Ile Gly Pro Pro Gly Pro Thr Gly Pro Lys Gly Ile Ser Gly His
325 330 335

Pro Gly Glu Lys Gly Glu Arg Gly Leu Arg Gly Glu Pro Gly Pro Gln
340 345 350

Gly Ser Ala Gly Gln Arg Gly Glu Pro Gly Pro Lys Gly Asp Pro Gly
355 360 365

Glu Lys Ser His Trp Asn Gln Ser Trp Gly Leu Gly Arg Ala Leu Pro
370 375 380

Ala Gln Ala Pro Pro Ala Ser Phe Gly Ala Arg Gly Ala Asp Met Gln
385 390 395 400

Pro Thr Thr Gly Ser Trp Pro Pro Gly Ala Gly Thr Arg Glu Ala Glu
405 410 415

Gly Gly Gly Gly Pro
420

<210> 52
<211> 240
<212> PRT
<213> Homo sapiens

<400> 52
His Ala Ser Ala Ala Arg Ala Ala Ala Gly Ser Glu Pro Arg Thr Gly
1 5 10 15

Cys Gly Gly Ser Ser His Arg Val Pro Leu Gly Pro Ser Pro Ala Ser
20 25 30

Leu Ser Pro Gln Arg Asp Leu Phe Gly Pro Pro Gly Pro Pro Gly Ala
35 40 45

Glu Val Thr Ala Glu Thr Leu Leu His Glu Phe Gln Glu Leu Leu Lys
50 55 60

Glu Ala Thr Glu Arg Arg Phe Ser Gly Leu Leu Asp Pro Leu Leu Pro
65 70 75 80

Gln Gly Ala Gly Leu Arg Leu Val Gly Glu Ala Phe His Cys Arg Leu
85 90 95

Gln Gly Pro Arg Arg Val Asp Lys Arg Thr Leu Val Glu Leu His Gly
100 105 110

Phe Gln Ala Pro Ala Ala Gln Gly Ala Phe Leu Arg Gly Ser Gly Leu
115 120 125

Ser Leu Ala Ser Gly Arg Phe Thr Ala Pro Val Ser Gly Ile Phe Gln
130 135 140

Phe Ser Ala Ser Leu His Val Asp His Ser Glu Leu Gln Gly Lys Ala
145 150 155 160

Arg Leu Arg Ala Arg Asp Val Val Cys Val Leu Ile Cys Ile Glu Ser
165 170 175

Leu Cys Gln Arg His Thr Cys Leu Glu Ala Val Ser Gly Leu Glu Ser
180 185 190

Asn Ser Arg Val Phe Thr Leu Gln Val Gln Gly Leu Leu Gln Leu Gln
195 200 205

Ala Gly Gln Tyr Ala Ser Val Phe Val Asp Asn Gly Ser Gly Ala Val
210 215 220

Leu Thr Ile Gln Ala Gly Ser Ser Phe Ser Gly Leu Leu Leu Gly Thr
225 230 235 240

<210> 53
<211> 281
<212> PRT
<213> Homo sapiens

<400> 53
Met Gly Ser Arg Gly Gln Gly Leu Leu Leu Ala Tyr Cys Leu Leu Leu
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Ala Phe Ala Ser Gly Leu Val Leu Ser Arg Val Pro His Val Gln Gly
20 25 30

Glu Gln Gln Glu Trp Glu Gly Thr Glu Glu Leu Pro Ser Pro Pro Asp
35 40 45

His Ala Glu Arg Ala Glu Glu Gln His Glu Lys Tyr Arg Pro Ser Gln
50 55 60

Asp Gln Gly Leu Pro Ala Ser Arg Cys Leu Arg Cys Cys Asp Pro Gly
65 70 75 80

Thr Ser Met Tyr Pro Ala Thr Ala Val Pro Gln Ile Asn Ile Thr Ile
85 90 95

Leu Lys Gly Glu Lys Gly Asp Arg Gly Asp Arg Gly Leu Gln Gly Lys
100 105 110

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Tyr Gly Lys Thr Gly Ser Ala Gly Ala Arg Gly His Thr Gly Pro Lys
        115                 120                 125

Gly Gln Lys Gly Ser Met Gly Ala Pro Gly Glu Arg Cys Lys Ser His
    130                 135                 140

Tyr Ala Ala Phe Ser Val Gly Arg Lys Lys Pro Met His Ser Asn His
145                 150                 155                 160

Tyr Tyr Gln Thr Val Ile Phe Asp Thr Glu Phe Val Asn Leu Tyr Asp
                165                 170                 175

His Phe Asn Met Phe Thr Gly Lys Phe Tyr Cys Tyr Val Pro Gly Leu
            180                 185                 190

Tyr Phe Phe Ser Leu Asn Val His Thr Trp Asn Gln Lys Glu Thr Tyr
        195                 200                 205

Leu His Ile Met Lys Asn Glu Glu Glu Val Ala Ile Leu Phe Ala Gln
    210                 215                 220

Val Gly Asp Arg Ser Ile Met Gln Ser Gln Ser Leu Met Leu Glu Leu
225                 230                 235                 240

Arg Glu Gln Asp Gln Val Trp Val Arg Leu Tyr Lys Gly Glu Arg Glu
                245                 250                 255

Asn Ala Ile Phe Ser Glu Glu Leu Asp Thr Tyr Ile Thr Phe Ser Gly
            260                 265                 270

Tyr Leu Val Lys His Ala Thr Glu Pro
        275                 280


<210> 54
<211> 205
<212> PRT
<213> Homo sapiens

<400> 54
Met Leu Gly Ala Lys Pro His Trp Leu Pro Gly Pro Leu His Ser Pro
  1               5                  10                  15

Gly Leu Pro Leu Val Leu Val Leu Leu Ala Leu Gly Ala Gly Trp Ala
             20                  25                  30

Gln Glu Gly Ser Glu Pro Val Leu Leu Glu Gly Glu Cys Leu Val Val
        35                  40                  45

Cys Glu Pro Gly Arg Ala Ala Ala Gly Gly Pro Gly Gly Ala Ala Leu
    50                  55                  60

Gly Glu Ala Pro Pro Gly Arg Val Ala Phe Ala Ala Val Arg Ser His
 65                  70                  75                  80

His His Glu Pro Ala Gly Glu Thr Gly Asn Gly Thr Ser Gly Ala Ile
                 85                  90                  95

Tyr Phe Asp Gln Val Leu Val Asn Glu Gly Gly Gly Phe Asp Arg Ala
            100                 105                 110

Ser Gly Ser Phe Val Ala Pro Val Arg Gly Val Tyr Ser Phe Arg Phe
        115                 120                 125

His Val Val Lys Val Tyr Asn Arg Gln Thr Val Gln Val Ser Leu Met
    130                 135                 140
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Leu Asn Thr Trp Pro Val Ile Ser Ala Phe Ala Asn Asp Pro Asp Val
145 150 155 160

Thr Arg Glu Ala Ala Thr Ser Ser Val Leu Leu Pro Leu Asp Pro Gly
165 170 175

Asp Arg Val Ser Leu Arg Leu Arg Arg Gly Asn Leu Leu Gly Gly Trp
180 185 190

Lys Tyr Ser Ser Phe Ser Gly Phe Leu Ile Phe Pro Leu
195 200 205

<210> 55
<211> 189
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (9)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 55
Leu Ala Leu Leu Leu Leu Leu Leu Xaa Ala Cys Cys Pro Val Arg Ala
1 5 10 15

Gln Asn Asp Thr Glu Pro Ile Val Leu Glu Gly Lys Cys Leu Val Val
20 25 30

Cys Asp Ser Ser Pro Ser Ala Asp Gly Ala Val Thr Ser Ser Leu Gly
35 40 45

Ile Ser Val Arg Ser Gly Ser Ala Lys Val Ala Phe Ser Ala Thr Arg
50 55 60

Ser Thr Asn His Glu Pro Ser Glu Met Ser Asn Arg Thr Met Thr Ile
65 70 75 80

Tyr Phe Asp Gln Val Leu Val Asn Ile Gly Asn His Phe Asp Leu Ala
85 90 95

Ser Ser Ile Phe Val Ala Pro Arg Lys Gly Ile Tyr Ser Phe Ser Phe
100 105 110

His Val Val Lys Val Tyr Asn Arg Gln Thr Ile Gln Val Ser Leu Met
115 120 125

Gln Asn Gly Tyr Pro Val Ile Ser Ala Phe Ala Gly Asp Gln Asp Val
130 135 140

Thr Arg Glu Ala Ala Ser Asn Gly Val Leu Leu Leu Met Glu Arg Glu
145 150 155 160

Asp Lys Val His Leu Lys Leu Glu Arg Gly Asn Leu Met Gly Gly Trp
165 170 175

Lys Tyr Ser Thr Phe Ser Gly Phe Leu Val Phe Pro Leu
180 185

<210> 56
<211> 201
<212> PRT

<213> Homo sapiens

<400> 56
Ser Gln Gly Leu Pro Gly Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala
1 5 10 15

Pro Gly Ala Pro Gly Glu Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro
20 25 30

Gly Pro Arg Gly Asp Pro Gly Pro Arg Gly Glu Ala Gly Pro Ala Gly
35 40 45

Pro Thr Gly Pro Ala Gly Glu Cys Ser Val Pro Pro Arg Ser Ala Phe
50 55 60

Ser Ala Lys Arg Ser Glu Ser Arg Val Pro Pro Pro Ser Asp Ala Pro
65 70 75 80

Leu Pro Phe Asp Arg Val Leu Val Asn Glu Gln Gly His Tyr Asp Ala
85 90 95

Val Thr Gly Lys Phe Thr Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala
100 105 110

Val His Ala Thr Val Tyr Arg Ala Ser Leu Gln Phe Asp Leu Val Lys
115 120 125

Asn Gly Glu Ser Ile Ala Ser Phe Phe Gln Phe Phe Gly Gly Trp Pro
130 135 140

Lys Pro Ala Ser Leu Ser Gly Gly Ala Met Val Arg Leu Glu Pro Glu
145 150 155 160

Asp Gln Val Trp Val Gln Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr
165 170 175

Ala Ser Ile Lys Thr Asp Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser
180 185 190

Asp Trp His Ser Ser Pro Val Phe Ala
195 200

<210> 57
<211> 245
<212> PRT
<213> Homo sapiens

<400> 57
Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu
1 5 10 15

Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys
20 25 30

Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp
35 40 45

Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala
50 55 60

Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Leu
65 70 75 80

Pro Gly His Pro Gly Lys Asn Gly Pro Met Gly Pro Pro Gly Met Pro
85 90 95

```
Gly Val Pro Gly Pro Met Gly Ile Pro Gly Glu Pro Gly Glu Glu Gly
            100                 105                 110

Arg Tyr Lys Gln Lys Phe Gln Ser Val Phe Thr Val Thr Arg Gln Thr
        115                 120                 125

His Gln Pro Pro Ala Pro Asn Ser Leu Ile Arg Phe Asn Ala Val Leu
    130                 135                 140

Thr Asn Pro Gln Gly Asp Tyr Asp Thr Ser Thr Gly Lys Phe Thr Cys
145                 150                 155                 160

Lys Val Pro Gly Leu Tyr Tyr Phe Val Tyr His Ala Ser His Thr Ala
                165                 170                 175

Asn Leu Cys Val Leu Leu Tyr Arg Ser Gly Val Lys Val Val Thr Phe
            180                 185                 190

Cys Gly His Thr Ser Lys Thr Asn Gln Val Asn Ser Gly Gly Val Leu
        195                 200                 205

Leu Arg Leu Gln Val Gly Glu Glu Val Trp Leu Ala Val Asn Asp Tyr
    210                 215                 220

Tyr Asp Met Val Gly Ile Gln Gly Ser Asp Ser Val Phe Ser Gly Phe
225                 230                 235                 240

Leu Leu Phe Pro Asp
                245


<210> 58
<211> 278
<212> PRT
<213> Homo sapiens

<400> 58
Met Gln Trp Leu Arg Val Arg Glu Ser Pro Gly Glu Ala Thr Gly His
  1               5                  10                  15

Arg Val Thr Met Gly Thr Ala Ala Leu Gly Pro Val Trp Ala Ala Leu
             20                  25                  30

Leu Leu Phe Leu Leu Met Cys Glu Ile Pro Met Val Glu Leu Thr Phe
         35                  40                  45

Asp Arg Ala Val Ala Ser Asp Cys Gln Arg Cys Cys Asp Ser Glu Asp
     50                  55                  60

Pro Leu Asp Pro Ala His Val Ser Ser Ala Ser Ser Ser Gly Arg Pro
 65                  70                  75                  80

His Ala Leu Pro Glu Ile Arg Pro Tyr Ile Asn Ile Thr Ile Leu Lys
                 85                  90                  95

Gly Asp Lys Gly Asp Pro Gly Pro Met Gly Leu Pro Gly Tyr Met Gly
            100                 105                 110

Arg Glu Gly Pro Gln Gly Glu Pro Gly Pro Gln Gly Ser Lys Gly Asp
        115                 120                 125

Lys Gly Glu Met Gly Ser Pro Gly Ala Pro Cys Gln Lys Arg Phe Phe
    130                 135                 140

Ala Phe Ser Val Gly Arg Lys Thr Ala Leu His Ser Gly Glu Asp Phe
```

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145                 150                 155                 160

Gln Thr Leu Leu Phe Glu Arg Val Phe Val Asn Leu Asp Gly Cys Phe
                165                 170                 175

Asp Met Ala Thr Gly Gln Phe Ala Ala Pro Leu Arg Gly Ile Tyr Phe
            180                 185                 190

Phe Ser Leu Asn Val His Ser Trp Asn Tyr Lys Glu Thr Tyr Val His
        195                 200                 205

Ile Met His Asn Gln Lys Glu Ala Val Ile Leu Tyr Ala Gln Pro Ser
    210                 215                 220

Glu Arg Ser Ile Met Gln Ser Gln Ser Val Met Leu Asp Leu Ala Tyr
225                 230                 235                 240

Gly Asp Arg Val Trp Val Arg Leu Phe Lys Arg Gln Arg Glu Asn Ala
                245                 250                 255

Ile Tyr Ser Asn Asp Phe Asp Thr Tyr Ile Thr Phe Ser Gly His Leu
            260                 265                 270

Ile Lys Ala Glu Asp Asp
        275


<210> 59
<211> 289
<212> PRT
<213> Homo sapiens

<400> 59
Met Phe Val Leu Leu Tyr Val Thr Ser Phe Ala Ile Cys Ala Ser Gly
1               5                   10                  15

Gln Pro Arg Gly Asn Gln Leu Lys Gly Glu Asn Tyr Ser Pro Arg Tyr
            20                  25                  30

Ile Cys Ser Ile Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Ala
        35                  40                  45

Asn Gly Ser Pro Gly Pro His Gly Arg Ile Gly Leu Pro Gly Arg Asp
    50                  55                  60

Gly Arg Asp Gly Arg Lys Gly Glu Lys Gly Glu Lys Gly Thr Ala Gly
65                  70                  75                  80

Leu Arg Gly Lys Thr Gly Pro Leu Gly Leu Ala Gly Glu Lys Gly Asp
                85                  90                  95

Gln Gly Glu Thr Gly Lys Lys Gly Pro Ile Gly Pro Glu Gly Glu Lys
            100                 105                 110

Gly Glu Val Gly Pro Ile Gly Pro Pro Gly Pro Lys Gly Asp Arg Gly
        115                 120                 125

Glu Gln Gly Asp Pro Gly Leu Pro Gly Val Cys Arg Cys Gly Ser Ile
    130                 135                 140

Val Leu Lys Ser Ala Phe Ser Val Gly Ile Thr Thr Ser Tyr Pro Glu
145                 150                 155                 160

Glu Arg Leu Pro Ile Ile Phe Asn Lys Val Leu Phe Asn Glu Gly Glu
                165                 170                 175
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His Tyr Asn Pro Ala Thr Gly Lys Phe Ile Cys Ala Phe Pro Gly Ile
            180                 185                 190

Tyr Tyr Phe Ser Tyr Asp Ile Thr Leu Ala Asn Lys His Leu Ala Ile
        195                 200                 205

Gly Leu Val His Asn Gly Gln Tyr Arg Ile Lys Thr Phe Asp Ala Asn
    210                 215                 220

Thr Gly Asn His Asp Val Ala Ser Gly Ser Thr Val Ile Tyr Leu Gln
225                 230                 235                 240

Pro Glu Asp Glu Val Trp Leu Glu Ile Phe Phe Thr Asp Gln Asn Gly
                245                 250                 255

Leu Phe Ser Asp Pro Gly Trp Ala Asp Ser Leu Phe Ser Gly Phe Leu
            260                 265                 270

Leu Tyr Val Asp Thr Asp Tyr Leu Asp Ser Ile Ser Glu Asp Asp Glu
        275                 280                 285

Leu



<210> 60
<211> 285
<212> PRT
<213> Homo sapiens

<400> 60
Met Ile Pro Trp Val Leu Leu Ala Cys Ala Leu Pro Cys Ala Ala Asp
1               5                   10                  15

Pro Leu Leu Gly Ala Phe Ala Arg Arg Asp Phe Arg Lys Gly Ser Pro
            20                  25                  30

Gln Leu Val Cys Ser Leu Pro Gly Pro Gln Gly Pro Pro Gly Pro Pro
        35                  40                  45

Gly Ala Pro Gly Pro Ser Gly Met Met Gly Arg Met Gly Phe Pro Gly
    50                  55                  60

Lys Asp Gly Gln Asp Gly His Asp Gly Asp Arg Gly Asp Ser Gly Glu
65                  70                  75                  80

Glu Gly Pro Pro Gly Arg Thr Gly Asn Arg Gly Lys Pro Gly Pro Lys
                85                  90                  95

Gly Lys Ala Gly Ala Ile Gly Arg Ala Gly Pro Arg Gly Pro Lys Gly
            100                 105                 110

Val Asn Gly Thr Pro Gly Lys His Gly Thr Pro Gly Lys Lys Gly Pro
        115                 120                 125

Lys Gly Lys Lys Gly Glu Pro Gly Leu Pro Gly Pro Cys Ser Cys Gly
    130                 135                 140

Ser Gly His Thr Lys Ser Ala Phe Ser Val Ala Val Thr Lys Ser Tyr
145                 150                 155                 160

Pro Arg Glu Arg Leu Pro Ile Lys Phe Asp Lys Ile Leu Met Asn Glu
                165                 170                 175

Gly Gly His Tyr Asn Ala Ser Ser Gly Lys Phe Val Cys Gly Val Pro
            180                 185                 190
```

```
Gly Ile Tyr Tyr Phe Thr Tyr Asp Ile Thr Leu Ala Asn Lys His Leu
        195                 200                 205

Ala Ile Gly Leu Val His Asn Gly Gln Tyr Arg Ile Arg Thr Phe Asp
    210                 215                 220

Ala Asn Thr Gly Asn His Asp Val Ala Ser Gly Ser Thr Ile Leu Ala
225                 230                 235                 240

Leu Lys Gln Gly Asp Glu Val Trp Leu Gln Ile Phe Tyr Ser Glu Gln
                245                 250                 255

Asn Gly Leu Phe Tyr Asp Pro Tyr Trp Thr Asp Ser Leu Phe Thr Gly
            260                 265                 270

Phe Leu Ile Tyr Ala Asp Gln Asp Asp Pro Asn Glu Val
        275                 280                 285


<210> 61
<211> 146
<212> PRT
<213> Homo sapiens

<400> 61
Thr Arg Ser Leu Val Gly Ser Asp Ala Gly Pro Gly Pro Arg His Gln
  1               5                  10                  15

Pro Leu Ala Phe Asp Thr Glu Phe Val Asn Ile Gly Gly Asp Phe Asp
             20                  25                  30

Ala Ala Ala Gly Val Phe Arg Cys Arg Leu Pro Gly Ala Tyr Phe Phe
         35                  40                  45

Ser Phe Thr Leu Gly Lys Leu Pro Arg Lys Thr Leu Ser Val Lys Leu
     50                  55                  60

Met Lys Asn Arg Asp Glu Val Gln Ala Met Ile Tyr Asp Asp Gly Ala
 65                  70                  75                  80

Ser Arg Arg Arg Glu Met Gln Ser Gln Ser Val Met Leu Ala Leu Arg
                 85                  90                  95

Arg Gly Asp Ala Val Trp Leu Leu Ser His Asp His Asp Gly Tyr Gly
            100                 105                 110

Ala Tyr Ser Asn His Gly Lys Tyr Ile Thr Phe Ser Gly Phe Leu Val
        115                 120                 125

Tyr Pro Asp Leu Ala Pro Ala Ala Pro Pro Gly Leu Gly Ala Ser Glu
    130                 135                 140

Leu Leu
145


<210> 62
<211> 251
<212> PRT
<213> Homo sapiens

<400> 62
Met Lys Ile Pro Trp Gly Ser Ile Pro Val Leu Met Leu Leu Leu Leu
  1               5                  10                  15
```

Leu Gly Leu Ile Asp Ile Ser Gln Ala Gln Leu Ser Cys Thr Gly Pro
20 25 30

Pro Ala Ile Pro Gly Ile Pro Gly Ile Pro Gly Thr Pro Gly Pro Asp
35 40 45

Gly Gln Pro Gly Thr Pro Gly Ile Lys Gly Glu Lys Gly Leu Pro Gly
50 55 60

Leu Ala Gly Asp His Gly Glu Phe Gly Glu Lys Gly Asp Pro Gly Ile
65 70 75 80

Pro Gly Asn Pro Gly Lys Val Gly Pro Lys Gly Pro Met Gly Pro Lys
85 90 95

Gly Gly Pro Gly Ala Pro Gly Ala Pro Gly Pro Lys Gly Glu Ser Gly
100 105 110

Asp Tyr Lys Ala Thr Gln Lys Ile Ala Phe Ser Ala Thr Arg Thr Ile
115 120 125

Asn Val Pro Leu Arg Arg Asp Gln Thr Ile Arg Phe Asp His Val Ile
130 135 140

Thr Asn Met Asn Asn Asn Tyr Glu Pro Arg Ser Gly Lys Phe Thr Cys
145 150 155 160

Lys Val Pro Gly Leu Tyr Tyr Phe Thr Tyr His Ala Ser Ser Arg Gly
165 170 175

Asn Leu Cys Val Asn Leu Met Arg Gly Arg Glu Arg Ala Gln Lys Val
180 185 190

Val Thr Phe Cys Asp Tyr Ala Tyr Asn Thr Phe Gln Val Thr Thr Gly
195 200 205

Gly Met Val Leu Lys Leu Glu Gln Gly Glu Asn Val Phe Leu Gln Ala
210 215 220

Thr Asp Lys Asn Ser Leu Leu Gly Met Glu Gly Ala Asn Ser Ile Phe
225 230 235 240

Ser Gly Phe Leu Leu Phe Pro Asp Met Glu Ala
245 250

<210> 63
<211> 975
<212> PRT
<213> Homo sapiens

<400> 63
Met Pro Cys Pro Ser Ala Leu Val Tyr Arg Val Asn Phe Arg Pro Arg
1 5 10 15

Tyr Val Thr Arg Tyr Lys Thr Val Thr Gln Leu Glu Trp Arg Cys Cys
20 25 30

Pro Gly Phe Arg Gly Gly Asp Cys Gln Glu Gly Pro Lys Asp Pro Val
35 40 45

Lys Thr Leu Arg Pro Thr Pro Ala Arg Pro Arg Asn Ser Leu Lys Lys
50 55 60

Ala Thr Asp Asn Glu Pro Ser Gln Phe Ser Glu Pro Arg Lys Thr Leu

65 70 75 80

Ser Pro Thr Gly Thr Ala Gln Pro Ser Trp Gly Val Asp Pro Lys Glu
85 90 95

Gly Pro Gln Glu Leu Gln Glu Lys Lys Ile Gln Val Leu Glu Glu Lys
100 105 110

Val Leu Arg Leu Thr Arg Thr Val Leu Asp Leu Gln Ser Ser Leu Ala
115 120 125

Gly Val Ser Glu Asn Leu Lys His Ala Thr Gln Asp Asp Ala Ser Arg
130 135 140

Thr Arg Ala Pro Gly Leu Ser Ser Gln His Pro Lys Pro Asp Thr Thr
145 150 155 160

Val Ser Gly Asp Thr Glu Thr Gly Gln Ser Pro Gly Val Phe Asn Thr
165 170 175

Lys Glu Ser Gly Met Lys Asp Ile Lys Ser Glu Leu Ala Glu Val Lys
180 185 190

Asp Thr Leu Lys Asn Lys Ser Asp Lys Leu Glu Glu Leu Asp Gly Lys
195 200 205

Val Lys Gly Tyr Glu Gly Gln Leu Arg Gln Leu Gln Glu Ala Ala Gln
210 215 220

Gly Pro Thr Val Thr Met Thr Thr Asn Glu Leu Tyr Gln Ala Tyr Val
225 230 235 240

Asp Ser Lys Ile Asp Ala Leu Arg Glu Glu Leu Met Glu Gly Met Asp
245 250 255

Arg Lys Leu Ala Asp Leu Lys Asn Ser Cys Glu Tyr Lys Leu Thr Gly
260 265 270

Leu Gln Gln Gln Cys Asp Asp Tyr Gly Ser Ser Tyr Leu Gly Val Ile
275 280 285

Glu Leu Ile Gly Glu Lys Glu Thr Ser Leu Arg Lys Glu Ile Asn Asn
290 295 300

Leu Arg Ala Arg Leu Gln Glu Pro Ser Ala Gln Ala Asn Cys Cys Asp
305 310 315 320

Ser Glu Lys Asn Gly Asp Ile Gly Gln Gln Ile Lys Thr Leu Asp Gln
325 330 335

Lys Ile Glu Arg Val Ala Glu Ala Thr Arg Met Leu Asn Gly Arg Leu
340 345 350

Asp Asn Glu Phe Asp Arg Leu Ile Val Pro Glu Pro Asp Val Asp Phe
355 360 365

Asp Ala Lys Trp Asn Glu Leu Asp Ala Arg Ile Asn Val Thr Glu Lys
370 375 380

Asn Ala Glu Glu His Cys Phe Tyr Ile Glu Glu Thr Leu Arg Gly Ala
385 390 395 400

Ile Asn Gly Glu Val Gly Asp Leu Lys Gln Leu Val Asp Gln Lys Ile
405 410 415

Gln Ser Leu Glu Asp Arg Leu Gly Ser Val Leu Leu Gln Met Thr Asn
420 425 430

```
Asn Thr Gly Ala Glu Leu Ser Pro Pro Gly Ala Ala Ala Leu Pro Gly
        435                 440                 445

Val Ser Gly Ser Gly Asp Glu Arg Val Met Met Glu Leu Asn His Leu
    450                 455                 460

Lys Asp Lys Val Gln Val Val Glu Asp Ile Cys Leu Leu Asn Ile Gln
465                 470                 475                 480

Gly Lys Pro His Gly Met Glu Gly Ala Leu Pro Asn Arg Glu Asp Arg
                485                 490                 495

Ala Val Arg Asp Ser Leu His Leu Leu Lys Ser Leu Asn Asp Thr Met
            500                 505                 510

His Arg Lys Phe Gln Glu Thr Glu Gln Thr Ile Gln Lys Leu Gln Gln
        515                 520                 525

Asp Phe Ser Phe Leu Tyr Ser Gln Leu Asn His Thr Glu Asn Asp Val
    530                 535                 540

Thr His Leu Gln Lys Glu Met Ser Asn Cys Arg Ala Gly Glu Asn Ala
545                 550                 555                 560

Gly Met Gly Arg Phe Thr Lys Val Gly Glu Gln Glu Arg Thr Val Asp
                565                 570                 575

Thr Leu Pro Ser Pro Gln His Pro Val Ala His Cys Cys Ser Gln Leu
            580                 585                 590

Glu Glu Arg Trp Gln Arg Leu Gln Ser Gln Val Ile Ser Glu Leu Asp
        595                 600                 605

Ala Cys Lys Glu Cys Thr Gln Gly Val Gln Arg Glu Val Ser Met Val
    610                 615                 620

Glu Gly Arg Val Ser His Met Glu Lys Thr Cys Ser Lys Leu Asp Ser
625                 630                 635                 640

Ile Ser Gly Asn Leu Gln Arg Ile Lys Glu Gly Leu Asn Lys His Val
                645                 650                 655

Ser Ser Leu Trp Asn Cys Val Arg Gln Met Asn Gly Thr Leu Arg Ser
            660                 665                 670

His Ser Arg Asp Ile Ser Gly Leu Lys Asn Ser Val Gln Gln Phe Tyr
        675                 680                 685

Ser His Val Phe Gln Ile Ser Thr Asp Leu Gln Asp Leu Val Lys Phe
    690                 695                 700

Gln Pro Ser Ala Lys Ala Pro Ser Pro Pro Pro Pro Ala Glu Ala Pro
705                 710                 715                 720

Lys Glu Pro Leu Gln Pro Glu Pro Ala Pro Pro Arg Pro Ser Gly Pro
                725                 730                 735

Ala Thr Ala Glu Asp Pro Gly Arg Arg Pro Val Leu Pro Gln Arg Pro
            740                 745                 750

Pro Glu Glu Arg Pro Pro Gln Pro Pro Gly Ser Thr Gly Val Ile Ala
        755                 760                 765

Glu Thr Gly Gln Ala Gly Pro Pro Ala Gly Ala Gly Val Ser Gly Arg
    770                 775                 780
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Gly Leu Pro Arg Gly Val Asp Gly Gln Thr Gly Ser Gly Thr Val Pro
785                 790                 795                 800

Gly Ala Glu Gly Phe Ala Gly Ala Pro Gly Tyr Pro Lys Ser Pro Pro
                805                 810                 815

Val Ala Ser Pro Gly Ala Pro Val Pro Ser Leu Val Ser Phe Ser Ala
            820                 825                 830

Gly Leu Thr Gln Lys Pro Phe Pro Ser Asp Gly Gly Val Val Leu Phe
        835                 840                 845

Asn Lys Val Leu Val Asn Asp Gly Asp Val Tyr Asn Pro Ser Thr Gly
    850                 855                 860

Val Phe Thr Ala Pro Tyr Asp Gly Arg Tyr Leu Ile Thr Ala Thr Leu
865                 870                 875                 880

Thr Pro Glu Arg Asp Ala Tyr Val Glu Ala Val Leu Ser Val Ser Asn
                885                 890                 895

Ala Ser Val Ala Gln Leu His Thr Ala Gly Tyr Arg Arg Glu Phe Leu
            900                 905                 910

Glu Tyr His Arg Pro Pro Gly Ala Leu His Thr Cys Gly Gly Pro Gly
        915                 920                 925

Ala Phe His Leu Ile Val His Leu Lys Ala Gly Asp Ala Val Asn Val
    930                 935                 940

Val Val Thr Gly Gly Lys Leu Ala His Thr Asp Phe Asp Glu Met Tyr
945                 950                 955                 960

Ser Thr Phe Ser Gly Val Phe Leu Tyr Pro Phe Leu Ser His Leu
                965                 970                 975


<210> 64
<211> 158
<212> PRT
<213> Homo sapiens

<400> 64
Met Thr Pro Val Asp Val Pro Val Thr Asn Pro Ala Ala Thr Ile Leu
  1               5                  10                  15

Pro Val His Val Tyr Pro Leu Pro Gln Gln Met Arg Val Ala Phe Ser
            20                  25                  30

Ala Ala Arg Thr Ser Asn Leu Ala Pro Gly Thr Leu Asp Gln Pro Ile
        35                  40                  45

Val Phe Asp Leu Leu Leu Asn Asn Leu Gly Glu Thr Phe Asp Leu Gln
    50                  55                  60

Leu Gly Arg Phe Asn Cys Pro Val Asn Gly Thr Tyr Val Phe Ile Phe
 65                 70                  75                  80

His Met Leu Lys Leu Ala Val Asn Val Pro Leu Tyr Val Asn Leu Met
                85                  90                  95

Lys Asn Glu Glu Val Leu Val Ser Ala Tyr Ala Asn Asp Gly Ala Pro
            100                 105                 110

Asp His Glu Thr Ala Ser Asn His Ala Ile Leu Gln Leu Phe Gln Gly
        115                 120                 125
```

Asp Gln Ile Trp Leu Arg Leu His Arg Gly Ala Ile Tyr Gly Ser Ser
    130   135   140

Trp Lys Tyr Ser Thr Phe Ser Gly Tyr Leu Leu Tyr Gln Asp
145   150   155

<210> 65
<211> 605
<212> PRT
<213> Homo sapiens

<400> 65
Met Gly Tyr Leu Glu Leu Lys Glu Asn Gln Gly His Arg Asp Ile Gln
1   5   10   15

Glu Leu Glu Ser Gln Val Cys Leu Glu Cys Gln Gly Lys Pro Gly Ala
            20   25   30

Met Gly Met Pro Gly Ala Lys Gly Glu Ile Gly Gln Lys Gly Glu Ile
        35   40   45

Gly Pro Met Gly Ile Pro Gly Pro Gln Gly Pro Pro Gly Pro His Gly
    50   55   60

Leu Pro Gly Ile Gly Lys Pro Gly Gly Pro Gly Leu Pro Gly Gln Pro
65   70   75   80

Gly Pro Lys Gly Asp Arg Gly Pro Lys Gly Leu Pro Gly Pro Gln Gly
                85   90   95

Leu Arg Gly Pro Lys Gly Asp Lys Gly Phe Gly Met Pro Gly Ala Pro
            100   105   110

Gly Val Lys Gly Pro Pro Gly Met His Gly Pro Pro Gly Pro Val Gly
        115   120   125

Leu Pro Gly Val Gly Lys Pro Gly Val Thr Gly Phe Pro Gly Pro Gln
    130   135   140

Gly Pro Leu Gly Lys Pro Gly Ala Pro Gly Glu Pro Gly Pro Gln Gly
145   150   155   160

Pro Ile Gly Val Pro Gly Val Gln Gly Pro Pro Gly Ile Pro Gly Ile
                165   170   175

Gly Lys Pro Gly Gln Asp Gly Ile Pro Gly Gln Pro Gly Phe Pro Gly
            180   185   190

Gly Lys Gly Glu Gln Gly Leu Pro Gly Leu Pro Gly Pro Pro Gly Leu
        195   200   205

Pro Gly Ile Gly Lys Pro Gly Phe Pro Gly Pro Lys Gly Asp Arg Gly
    210   215   220

Met Gly Gly Val Pro Gly Ala Leu Gly Pro Arg Gly Glu Lys Gly Pro
225   230   235   240

Ile Gly Ala Pro Gly Ile Gly Gly Pro Pro Gly Glu Pro Gly Leu Pro
                245   250   255

Gly Ile Pro Gly Pro Met Gly Pro Pro Gly Ala Ile Gly Phe Pro Gly
            260   265   270

Pro Lys Gly Glu Gly Gly Ile Val Gly Pro Gln Gly Pro Pro Gly Pro

275 280 285

Lys Gly Glu Pro Gly Leu Gln Gly Phe Pro Gly Lys Pro Gly Phe Leu
290 295 300

Gly Glu Val Gly Pro Pro Gly Met Arg Gly Leu Pro Gly Pro Ile Gly
305 310 315 320

Pro Lys Gly Glu Ala Gly Gln Lys Gly Val Pro Gly Leu Pro Gly Val
325 330 335

Pro Gly Leu Leu Gly Pro Lys Gly Glu Pro Gly Ile Pro Gly Asp Gln
340 345 350

Gly Leu Gln Gly Pro Pro Gly Ile Pro Gly Ile Gly Gly Pro Ser Gly
355 360 365

Pro Ile Gly Pro Pro Gly Ile Pro Gly Pro Lys Gly Glu Pro Gly Leu
370 375 380

Pro Gly Pro Pro Gly Phe Pro Gly Ile Gly Lys Pro Gly Val Ala Gly
385 390 395 400

Leu His Gly Pro Pro Gly Lys Pro Gly Ala Leu Gly Pro Gln Gly Gln
405 410 415

Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro
420 425 430

Ala Val Met Pro Pro Thr Pro Pro Pro Gln Gly Glu Tyr Leu Pro Asp
435 440 445

Met Gly Leu Gly Ile Asp Gly Val Lys Pro Pro His Ala Tyr Gly Ala
450 455 460

Lys Lys Gly Lys Asn Gly Gly Pro Ala Tyr Glu Met Pro Ala Phe Thr
465 470 475 480

Ala Glu Leu Thr Ala Pro Phe Pro Pro Val Gly Ala Pro Val Lys Phe
485 490 495

Asn Lys Leu Leu Tyr Asn Gly Arg Gln Asn Tyr Asn Pro Gln Thr Gly
500 505 510

Ile Phe Thr Cys Glu Val Pro Gly Val Tyr Tyr Phe Ala Tyr His Val
515 520 525

His Cys Lys Gly Gly Asn Val Trp Val Ala Leu Phe Lys Asn Asn Glu
530 535 540

Pro Val Met Tyr Thr Tyr Asp Glu Tyr Lys Lys Gly Phe Leu Asp Gln
545 550 555 560

Ala Ser Gly Ser Ala Val Leu Leu Leu Arg Pro Gly Asp Arg Val Phe
565 570 575

Leu Gln Met Pro Ser Glu Gln Ala Ala Gly Leu Tyr Ala Gly Gln Tyr
580 585 590

Val His Ser Ser Phe Ser Gly Tyr Leu Leu Tyr Pro Met
595 600 605

<210> 66
<211> 194
<212> PRT

<213> Homo sapiens

<400> 66
Arg Gly Pro Trp Leu Pro Trp Asn Thr Gly Pro Pro Gly Pro Pro Gly
1 5 10 15

Pro Pro Gly Pro Pro Gly Ala Pro Gly Ala Phe Asp Glu Thr Gly Ile
20 25 30

Ala Gly Leu His Leu Pro Asn Gly Gly Val Glu Gly Ala Val Leu Gly
35 40 45

Lys Gly Gly Lys Pro Gln Phe Gly Leu Gly Glu Leu Ser Ala His Ala
50 55 60

Thr Pro Ala Phe Thr Ala Val Leu Thr Ser Pro Phe Pro Ala Ser Gly
65 70 75 80

Met Pro Val Lys Phe Asp Arg Thr Leu Tyr Asn Gly His Ser Gly Tyr
85 90 95

Asn Pro Ala Thr Gly Ile Phe Thr Cys Pro Val Gly Gly Val Tyr Tyr
100 105 110

Phe Ala Tyr His Val His Val Lys Gly Thr Asn Val Trp Val Ala Leu
115 120 125

Tyr Lys Asn Asn Val Pro Ala Thr Tyr Thr Tyr Asp Glu Tyr Lys Lys
130 135 140

Gly Tyr Leu Asp Gln Ala Ser Gly Gly Ala Val Leu Gln Leu Arg Pro
145 150 155 160

Asn Asp Gln Val Trp Val Gln Met Pro Ser Asp Gln Ala Asn Gly Leu
165 170 175

Tyr Ser Thr Glu Tyr Ile His Ser Ser Phe Ser Gly Phe Leu Leu Cys
180 185 190

Pro Thr

<210> 67
<211> 244
<212> PRT
<213> Homo sapiens

<400> 67
Met Leu Leu Leu Gly Ala Val Leu Leu Leu Leu Ala Leu Pro Gly His
1 5 10 15

Asp Gln Glu Thr Thr Thr Gln Gly Pro Gly Val Leu Leu Pro Leu Pro
20 25 30

Lys Gly Ala Cys Thr Gly Trp Met Ala Gly Ile Pro Gly His Pro Gly
35 40 45

His Asn Gly Ala Pro Gly Arg Asp Gly Arg Asp Gly Thr Pro Gly Glu
50 55 60

Lys Gly Glu Lys Gly Asp Pro Gly Leu Ile Gly Pro Lys Gly Asp Ile
65 70 75 80

Gly Glu Thr Gly Val Pro Gly Ala Glu Gly Pro Arg Gly Phe Pro Gly
85 90 95

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Ile Gln Gly Arg Lys Gly Glu Pro Gly Glu Gly Ala Tyr Val Tyr Arg
            100                 105                 110

Ser Ala Phe Ser Val Gly Leu Glu Thr Tyr Val Thr Ile Pro Asn Met
        115                 120                 125

Pro Ile Arg Phe Thr Lys Ile Phe Tyr Asn Gln Gln Asn His Tyr Asp
    130                 135                 140

Gly Ser Thr Gly Lys Phe His Cys Asn Ile Pro Gly Leu Tyr Tyr Phe
145                 150                 155                 160

Ala Tyr His Ile Thr Val Tyr Met Lys Asp Val Lys Val Ser Leu Phe
                165                 170                 175

Lys Lys Asp Lys Ala Met Leu Phe Thr Tyr Asp Gln Tyr Gln Glu Asn
            180                 185                 190

Asn Val Asp Gln Ala Ser Gly Ser Val Leu Leu His Leu Glu Val Gly
        195                 200                 205

Asp Gln Val Trp Leu Gln Val Tyr Gly Glu Gly Glu Arg Asn Gly Leu
    210                 215                 220

Tyr Ala Asp Asn Asp Asn Asp Ser Thr Phe Thr Gly Phe Leu Leu Tyr
225                 230                 235                 240

His Asp Thr Asn




<210> 68
<211> 361
<212> PRT
<213> Homo sapiens

<400> 68
Thr Arg Pro Asp Ser Leu Asn Glu Leu Gln Thr Thr Val Glu Gly Gln
1               5                   10                  15

Gly Ala Asp Leu Ala Asp Leu Gly Ala Thr Lys Asp Arg Ile Ile Ser
            20                  25                  30

Glu Ile Asn Arg Leu Gln Gln Glu Ala Thr Glu His Ala Thr Glu Ser
        35                  40                  45

Glu Glu Arg Phe Arg Gly Leu Glu Glu Gly Gln Ala Gln Ala Gly Gln
    50                  55                  60

Cys Pro Ser Leu Glu Gly Arg Leu Gly Arg Leu Glu Gly Val Cys Glu
65                  70                  75                  80

Arg Leu Asp Thr Val Ala Gly Gly Leu Gln Gly Leu Arg Glu Gly Leu
                85                  90                  95

Ser Arg His Val Ala Gly Leu Trp Ala Gly Leu Arg Glu Thr Asn Thr
            100                 105                 110

Thr Ser Gln Met Gln Ala Ala Leu Leu Glu Lys Leu Val Gly Gly Gln
        115                 120                 125

Ala Gly Leu Gly Arg Arg Leu Gly Ala Leu Asn Ser Ser Leu Gln Leu
    130                 135                 140

Leu Glu Asp Arg Leu His Gln Leu Ser Leu Lys Asp Leu Thr Gly Pro
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145                 150                 155                 160

Ala Gly Glu Ala Gly Pro Pro Gly Pro Pro Gly Leu Gln Gly Pro Pro
                165                 170                 175

Gly Pro Ala Gly Pro Pro Gly Ser Pro Gly Lys Asp Gly Gln Glu Gly
            180                 185                 190

Pro Ile Gly Pro Pro Gly Pro Gln Gly Glu Gln Gly Val Glu Gly Ala
        195                 200                 205

Pro Ala Ala Pro Val Pro Gln Val Ala Phe Ser Ala Ala Leu Ser Leu
    210                 215                 220

Pro Arg Ser Glu Pro Gly Thr Val Pro Phe Asp Arg Val Leu Leu Asn
225                 230                 235                 240

Asp Gly Gly Tyr Tyr Asp Pro Glu Thr Gly Val Phe Thr Ala Pro Leu
                245                 250                 255

Ala Gly Arg Tyr Leu Leu Ser Ala Val Leu Thr Gly His Arg His Glu
            260                 265                 270

Lys Val Glu Ala Val Leu Ser Arg Ser Asn Gln Gly Val Ala Arg Val
        275                 280                 285

Asp Ser Gly Gly Tyr Glu Pro Glu Gly Leu Glu Asn Lys Pro Val Ala
    290                 295                 300

Glu Ser Gln Pro Ser Pro Gly Thr Leu Gly Val Phe Ser Leu Ile Leu
305                 310                 315                 320

Pro Leu Gln Ala Gly Asp Thr Val Cys Val Asp Leu Val Met Gly Gln
                325                 330                 335

Leu Ala His Ser Glu Glu Pro Leu Thr Ile Phe Ser Gly Ala Leu Leu
            340                 345                 350

Tyr Gly Asp Pro Glu Leu Glu His Ala
        355                 360


<210> 69
<211> 333
<212> PRT
<213> Homo sapiens

<400> 69
Met Arg Ile Trp Trp Leu Leu Leu Ala Ile Glu Ile Cys Thr Gly Asn
  1               5                  10                  15

Ile Asn Ser Gln Asp Thr Cys Arg Gln Gly His Pro Gly Ile Pro Gly
             20                  25                  30

Asn Pro Gly His Asn Gly Leu Pro Gly Arg Asp Gly Arg Asp Gly Ala
         35                  40                  45

Lys Gly Asp Lys Gly Asp Ala Gly Glu Pro Gly Arg Pro Gly Ser Pro
     50                  55                  60

Gly Lys Asp Gly Thr Ser Gly Glu Lys Gly Glu Arg Gly Ala Asp Gly
 65                  70                  75                  80

Lys Val Glu Ala Lys Gly Ile Lys Gly Asp Gln Gly Ser Arg Gly Ser
                 85                  90                  95
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Pro Gly Lys His Gly Pro Lys Gly Leu Ala Gly Pro Met Gly Glu Lys
100 105 110

Gly Leu Arg Gly Glu Thr Gly Pro Gln Gly Gln Lys Gly Asn Lys Gly
115 120 125

Asp Val Gly Pro Thr Gly Pro Glu Gly Pro Arg Gly Asn Ile Gly Pro
130 135 140

Leu Gly Pro Thr Gly Leu Pro Gly Pro Met Gly Pro Ile Gly Lys Pro
145 150 155 160

Gly Pro Lys Gly Glu Ala Gly Pro Thr Gly Pro Gln Gly Glu Pro Gly
165 170 175

Val Arg Gly Ile Arg Gly Trp Lys Gly Asp Arg Gly Glu Lys Gly Lys
180 185 190

Ile Gly Glu Thr Leu Val Leu Pro Lys Ser Ala Phe Thr Val Gly Leu
195 200 205

Thr Val Leu Ser Lys Phe Pro Ser Ser Asp Val Pro Ile Lys Phe Asp
210 215 220

Lys Ile Leu Tyr Asn Glu Phe Asn His Tyr Asp Thr Ala Ala Gly Lys
225 230 235 240

Phe Thr Cys His Ile Ala Gly Val Tyr Tyr Phe Thr Tyr His Ile Thr
245 250 255

Val Phe Ser Arg Asn Val Gln Val Ser Leu Val Lys Asn Gly Val Lys
260 265 270

Ile Leu His Thr Lys Asp Ala Tyr Met Ser Ser Glu Asp Gln Ala Ser
275 280 285

Gly Gly Ile Val Leu Gln Leu Lys Leu Gly Asp Glu Val Trp Leu Gln
290 295 300

Val Thr Gly Gly Glu Arg Phe Asn Gly Leu Phe Ala Asp Glu Asp Asp
305 310 315 320

Asp Thr Thr Phe Thr Gly Phe Leu Leu Phe Ser Ser Pro
325 330

<210> 70
<211> 229
<212> PRT
<213> Homo sapiens

<400> 70
Met Asp Leu Leu Gln Phe Leu Ala Phe Leu Phe Val Leu Leu Leu Ser
1 5 10 15

Gly Met Gly Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser Leu
20 25 30

Glu Ile Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu Leu
35 40 45

Ala Leu Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr Lys
50 55 60

Ile Leu Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp Ser
65 70 75 80

Arg Thr Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Phe Pro
85 90 95

Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn Thr
100 105 110

Ala Phe Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His Tyr
115 120 125

Tyr Phe Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly Ile
130 135 140

Ser Phe Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser Pro
145 150 155 160

Ile Leu Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp Ser
165 170 175

Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro Ser
180 185 190

Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg Lys
195 200 205

Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser Arg
210 215 220

Ser Gln Ser Glu Leu
225

<210> 71
<211> 229
<212> PRT
<213> Homo sapiens

<400> 71
Met Asp Leu Leu Gln Phe Leu Ala Phe Leu Phe Val Leu Leu Leu Ser
1 5 10 15

Gly Met Gly Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser Leu
20 25 30

Glu Ile Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu Leu
35 40 45

Ala Leu Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr Lys
50 55 60

Ile Leu Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp Ser
65 70 75 80

Arg Thr Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Cys Pro
85 90 95

Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn Thr
100 105 110

Ala Phe Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His Tyr
115 120 125

Tyr Phe Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly Ile
130 135 140

Ser Phe Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser Pro

```
145                 150                 155                 160

Ile Leu Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp Ser
                165                 170                 175

Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro Ser
            180                 185                 190

Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg Lys
        195                 200                 205

Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser Arg
    210                 215                 220

Ser Gln Ser Glu Leu
225


<210> 72
<211> 459
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (321)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (345)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 72
Met Gly Gly Pro Arg Ala Trp Ala Leu Leu Cys Leu Gly Leu Leu Leu
  1               5                  10                  15

Pro Gly Gly Gly Ala Ala Trp Ser Ile Gly Ala Ala Pro Phe Ser Gly
             20                  25                  30

Arg Arg Asn Trp Cys Ser Tyr Val Val Thr Arg Thr Ile Ser Cys His
         35                  40                  45

Val Gln Asn Gly Thr Tyr Leu Gln Arg Val Leu Gln Asn Cys Pro Trp
     50                  55                  60

Pro Met Ser Cys Pro Gly Ser Ser Tyr Arg Thr Val Val Arg Pro Thr
 65                  70                  75                  80

Tyr Lys Val Met Tyr Lys Ile Val Thr Ala Arg Glu Trp Arg Cys Cys
                 85                  90                  95

Pro Gly His Ser Gly Val Ser Cys Glu Glu Val Ala Ala Ser Ser Ala
            100                 105                 110

Ser Leu Glu Pro Met Trp Ser Gly Ser Thr Met Arg Arg Met Ala Leu
        115                 120                 125

Arg Pro Thr Ala Phe Ser Gly Cys Leu Asn Cys Ser Lys Val Ser Glu
    130                 135                 140

Leu Thr Glu Arg Leu Lys Val Leu Glu Ala Lys Met Thr Met Leu Thr
145                 150                 155                 160

Val Ile Glu Gln Pro Val Pro Pro Thr Pro Ala Thr Pro Glu Asp Pro
                165                 170                 175
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Ala Pro Leu Trp Gly Pro Pro Pro Ala Gln Gly Ser Pro Gly Asp Gly
180 185 190

Gly Leu Gln Asp Gln Val Gly Ala Trp Gly Leu Pro Gly Pro Thr Gly
195 200 205

Pro Lys Gly Asp Ala Gly Ser Arg Gly Pro Met Gly Met Arg Gly Pro
210 215 220

Pro Gly Pro Gln Gly Pro Pro Gly Ser Pro Gly Arg Ala Gly Ala Val
225 230 235 240

Gly Thr Pro Gly Glu Arg Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly
245 250 255

Pro Pro Gly Pro Pro Ala Pro Val Gly Pro Pro His Ala Arg Ile Ser
260 265 270

Gln His Gly Asp Pro Leu Leu Ser Asn Thr Phe Thr Glu Thr Asn Asn
275 280 285

His Trp Pro Gln Gly Pro Thr Gly Pro Pro Gly Pro Pro Gly Pro Met
290 295 300

Gly Pro Pro Gly Pro Pro Gly Pro Thr Gly Val Pro Gly Ser Pro Gly
305 310 315 320

Xaa Ile Gly Pro Pro Gly Pro Thr Gly Pro Lys Gly Ile Ser Gly His
325 330 335

Pro Gly Glu Lys Gly Glu Lys Lys Xaa Leu Arg Gly Glu Pro Gly Pro
340 345 350

Gln Gly Ser Ala Gly Gln Arg Gly Glu Pro Gly Pro Lys Gly Asp Pro
355 360 365

Gly Glu Lys Ser His Trp Asn Gln Ser Trp Gly Leu Gly Gly Pro Cys
370 375 380

Arg His Arg His Pro Gln Pro Pro Ser Gly Gln Glu Gly Gly His Ala
385 390 395 400

Thr Asn Tyr Arg Asp Arg Gly Pro Gln Glu Pro Gly Arg Glu Arg Leu
405 410 415

Arg Val Val Ala Ala Pro Glu Ala Asp Gln Ala Arg Leu Pro Leu Leu
420 425 430

Pro Gly Leu Gly Gln Leu Pro Pro Gly Thr Ala Arg Pro Tyr Leu Leu
435 440 445

Met Ser Ser Gly Ser Leu Leu Pro Ser Arg Pro
450 455

<210> 73
<211> 443
<212> PRT
<213> Homo sapiens

<400> 73
Met Gly Gly Pro Arg Ala Trp Ala Leu Leu Cys Leu Gly Leu Leu Leu
1 5 10 15

Pro Gly Gly Gly Ala Ala Trp Ser Ile Gly Ala Ala Pro Phe Ser Gly

20 25 30

Arg Arg Asn Trp Cys Ser Tyr Val Val Thr Arg Thr Ile Ser Cys His
35 40 45

Val Gln Asn Gly Thr Tyr Leu Gln Arg Val Leu Gln Asn Cys Pro Trp
50 55 60

Pro Met Ser Cys Pro Gly Ser Ser Tyr Arg Thr Val Val Arg Pro Thr
65 70 75 80

Tyr Lys Val Met Tyr Lys Ile Val Thr Ala Arg Glu Trp Arg Cys Cys
85 90 95

Pro Gly His Ser Gly Val Ser Cys Glu Glu Val Ala Ala Ser Ser Ala
100 105 110

Ser Leu Glu Pro Met Trp Ser Gly Ser Thr Met Arg Arg Met Ala Leu
115 120 125

Arg Pro Thr Ala Phe Ser Gly Cys Leu Asn Cys Ser Lys Val Ser Glu
130 135 140

Leu Thr Glu Arg Leu Lys Val Leu Glu Ala Lys Met Thr Met Leu Thr
145 150 155 160

Val Ile Glu Gln Pro Val Pro Pro Thr Pro Ala Thr Pro Glu Asp Pro
165 170 175

Ala Pro Leu Trp Gly Pro Pro Pro Ala Gln Gly Ser Pro Gly Asp Gly
180 185 190

Gly Leu Gln Asp Gln Val Gly Ala Trp Gly Leu Pro Gly Pro Thr Gly
195 200 205

Pro Lys Gly Asp Ala Gly Ser Arg Gly Pro Met Gly Met Arg Gly Pro
210 215 220

Pro Gly Pro Gln Gly Pro Pro Gly Ser Pro Gly Arg Ala Gly Ala Val
225 230 235 240

Gly Thr Pro Gly Glu Arg Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly
245 250 255

Pro Pro Gly Pro Pro Ala Pro Val Gly Pro Pro His Ala Arg Ile Ser
260 265 270

Gln His Gly Asp Pro Leu Leu Ser Asn Thr Phe Thr Glu Thr Asn Asn
275 280 285

His Trp Pro Gln Gly Pro Thr Gly Pro Pro Gly Pro Pro Gly Pro Met
290 295 300

Gly Pro Pro Gly Pro Pro Gly Pro Thr Gly Val Pro Gly Ser Pro Gly
305 310 315 320

His Ile Gly Pro Pro Gly Pro Thr Gly Pro Lys Gly Ile Ser Gly His
325 330 335

Pro Gly Glu Lys Gly Glu Arg Gly Leu Arg Gly Glu Pro Gly Pro Gln
340 345 350

Gly Ser Ala Gly Gln Arg Gly Glu Pro Gly Pro Lys Gly Asp Pro Gly
355 360 365

Glu Lys Ser His Trp Gly Glu Gly Leu His Gln Leu Arg Glu Ala Leu
370 375 380

Lys Ile Leu Ala Glu Arg Val Leu Ile Leu Glu Thr Met Ile Gly Leu
385 390 395 400

Tyr Glu Pro Glu Leu Gly Ser Gly Ala Gly Pro Ala Gly Thr Gly Thr
405 410 415

Pro Ser Leu Leu Arg Gly Lys Arg Gly Gly His Ala Thr Asn Tyr Arg
420 425 430

Ile Val Ala Pro Arg Ser Arg Asp Glu Arg Gly
435 440

<210> 74
<211> 12
<212> PRT
<213> Homo sapiens

<400> 74
Gly Arg Pro Arg Pro Pro Ala Leu Val Leu Ala Arg
1 5 10

<210> 75
<211> 19
<212> PRT
<213> Homo sapiens

<400> 75
Gly Thr Ala Arg Pro Tyr Leu Leu Met Ser Ser Gly Ser Leu Leu Pro
1 5 10 15

Ser Arg Pro

<210> 76
<211> 421
<212> PRT
<213> Homo sapiens

<400> 76
Met Gly Gly Pro Arg Ala Trp Ala Leu Leu Cys Leu Gly Leu Leu Leu
1 5 10 15

Pro Gly Gly Gly Ala Ala Trp Ser Ile Gly Ala Ala Pro Phe Ser Gly
20 25 30

Arg Arg Asn Trp Cys Ser Tyr Val Val Thr Arg Thr Ile Ser Cys His
35 40 45

Val Gln Asn Gly Thr Tyr Leu Gln Arg Val Leu Gln Asn Cys Pro Trp
50 55 60

Pro Met Ser Cys Pro Gly Ser Ser Tyr Arg Thr Val Val Arg Pro Thr
65 70 75 80

Tyr Lys Val Met Tyr Lys Ile Val Thr Ala Arg Glu Trp Arg Cys Cys
85 90 95

Pro Gly His Ser Gly Val Ser Cys Glu Glu Val Ala Ala Ser Ser Ala
100 105 110

Ser Leu Glu Pro Met Trp Ser Gly Ser Thr Met Arg Arg Met Ala Leu
        115   120   125

Arg Pro Thr Ala Phe Ser Gly Cys Leu Asn Cys Ser Lys Val Ser Glu
    130   135   140

Leu Thr Glu Arg Leu Lys Val Leu Glu Ala Lys Met Thr Met Leu Thr
145   150   155   160

Val Ile Glu Gln Pro Val Pro Ser Thr Pro Ala Thr Pro Glu Asp Pro
                165   170   175

Ala Pro Leu Trp Gly Pro Pro Pro Ala Gln Gly Ser Pro Gly Asp Gly
            180   185   190

Gly Leu Gln Asp Gln Val Gly Ala Trp Gly Leu Pro Gly Pro Thr Gly
        195   200   205

Pro Lys Gly Asp Ala Gly Ser Arg Gly Pro Met Gly Met Arg Gly Pro
    210   215   220

Pro Gly Pro Gln Gly Pro Pro Gly Ser Pro Gly Arg Ala Gly Ala Val
225   230   235   240

Gly Thr Pro Gly Glu Arg Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly
                245   250   255

Pro Pro Gly Pro Pro Ala Pro Val Gly Pro Pro His Ala Arg Ile Ser
            260   265   270

Gln His Gly Asp Pro Leu Leu Ser Asn Thr Phe Thr Glu Thr Asn Asn
        275   280   285

His Trp Pro Gln Gly Pro Thr Gly Pro Pro Gly Pro Pro Gly Pro Met
    290   295   300

Gly Pro Pro Gly Pro Pro Gly Pro Thr Gly Val Pro Gly Ser Pro Gly
305   310   315   320

His Ile Gly Pro Pro Gly Pro Thr Gly Pro Lys Gly Ile Ser Gly His
                325   330   335

Pro Gly Glu Lys Gly Glu Arg Gly Leu Arg Gly Glu Pro Gly Pro Gln
            340   345   350

Gly Ser Ala Gly Gln Arg Gly Glu Pro Gly Pro Lys Gly Asp Pro Gly
        355   360   365

Glu Lys Ser His Trp Asn Gln Ser Trp Gly Leu Gly Arg Ala Leu Pro
    370   375   380

Ala Gln Ala Pro Pro Ala Ser Phe Gly Ala Arg Gly Ala Asp Met Gln
385   390   395   400

Pro Thr Thr Gly Ser Trp Pro Pro Gly Ala Gly Thr Arg Glu Ala Glu
                405   410   415

Gly Gly Gly Gly Pro
            420

<210> 77
<211> 421
<212> PRT
<213> Homo sapiens

<400> 77
Met Gly Gly Pro Arg Ala Trp Ala Leu Leu Cys Leu Gly Leu Leu Leu
1   5   10   15

Pro Gly Gly Gly Ala Ala Trp Ser Ile Gly Ala Ala Pro Phe Ser Gly
            20   25   30

Arg Arg Asn Trp Cys Ser Tyr Val Val Thr Arg Thr Ile Ser Cys His
        35   40   45

Val Gln Asn Gly Thr Tyr Leu Gln Arg Val Leu Gln Asn Cys Pro Trp
    50   55   60

Pro Met Ser Cys Pro Gly Ser Ser Tyr Arg Thr Val Val Arg Pro Thr
65   70   75   80

Tyr Lys Val Met Tyr Lys Ile Val Thr Ala Arg Glu Trp Arg Cys Cys
                85   90   95

Pro Gly His Ser Gly Val Ser Cys Glu Glu Val Ala Ala Ser Ser Ala
            100   105   110

Ser Leu Glu Pro Met Trp Ser Gly Ser Thr Met Arg Arg Met Ala Leu
        115   120   125

Arg Pro Thr Ala Phe Ser Gly Cys Leu Asn Cys Ser Lys Val Ser Glu
    130   135   140

Leu Thr Glu Arg Leu Lys Val Leu Glu Ala Lys Met Thr Met Leu Thr
145   150   155   160

Val Ile Glu Gln Pro Val Pro Pro Thr Pro Ala Thr Pro Glu Asp Pro
                165   170   175

Ala Pro Leu Trp Gly Pro Pro Pro Ala Gln Gly Ser Pro Gly Asp Gly
            180   185   190

Gly Leu Gln Asp Gln Val Gly Ala Trp Gly Leu Pro Gly Pro Thr Gly
        195   200   205

Pro Lys Gly Asp Ala Gly Ser Arg Gly Pro Met Gly Met Arg Gly Pro
    210   215   220

Pro Gly Pro Gln Gly Pro Pro Gly Ser Pro Gly Arg Ala Gly Ala Val
225   230   235   240

Gly Thr Pro Gly Glu Arg Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly
                245   250   255

Pro Pro Gly Pro Pro Ala Pro Val Gly Pro Pro His Ala Arg Ile Ser
            260   265   270

Gln His Gly Asp Pro Leu Leu Ser Asn Thr Phe Thr Glu Thr Asn Asn
        275   280   285

His Trp Pro Gln Gly Pro Thr Gly Pro Pro Gly Pro Pro Gly Pro Met
    290   295   300

Gly Pro Pro Gly Pro Pro Gly Pro Thr Gly Val Pro Gly Ser Pro Gly
305   310   315   320

His Ile Gly Pro Pro Gly Pro Thr Gly Pro Lys Gly Ile Ser Gly His
                325   330   335

Pro Gly Glu Lys Gly Glu Arg Gly Leu Arg Gly Glu Pro Gly Pro Gln
            340   345   350

Gly Ser Ala Gly Gln Arg Gly Glu Pro Gly Pro Lys Gly Asp Pro Gly
355 360 365

Glu Lys Ser His Trp Asn Gln Ser Trp Gly Leu Gly Arg Ala Leu Pro
370 375 380

Ala Gln Ala Pro Pro Ala Ser Phe Gly Ala Arg Gly Ala Asp Met Gln
385 390 395 400

Pro Thr Thr Gly Ser Trp Pro Pro Gly Ala Gly Thr Arg Glu Ala Glu
405 410 415

Gly Gly Gly Gly Pro
420

<210> 78
<211> 458
<212> PRT
<213> Homo sapiens

<400> 78
Met Gly Gly Pro Arg Ala Trp Ala Leu Leu Cys Leu Gly Leu Leu Leu
1 5 10 15

Pro Gly Gly Gly Ala Ala Trp Ser Ile Gly Ala Ala Pro Phe Ser Gly
20 25 30

Arg Arg Asn Trp Cys Ser Tyr Val Val Thr Arg Thr Ile Ser Cys His
35 40 45

Val Gln Asn Gly Thr Tyr Leu Gln Arg Val Leu Gln Asn Cys Pro Trp
50 55 60

Pro Met Ser Cys Pro Gly Ser Ser Tyr Arg Thr Val Val Arg Pro Thr
65 70 75 80

Tyr Lys Val Met Tyr Lys Ile Val Thr Ala Arg Glu Trp Arg Cys Cys
85 90 95

Pro Gly His Ser Gly Val Ser Cys Glu Glu Val Ala Ala Ser Ser Ala
100 105 110

Ser Leu Glu Pro Met Trp Ser Gly Ser Thr Met Arg Arg Met Ala Leu
115 120 125

Arg Pro Thr Ala Phe Ser Gly Cys Leu Asn Cys Ser Lys Val Ser Glu
130 135 140

Leu Thr Glu Arg Leu Lys Val Leu Glu Ala Lys Met Thr Met Leu Thr
145 150 155 160

Val Ile Glu Gln Pro Val Pro Pro Thr Pro Ala Thr Pro Glu Asp Pro
165 170 175

Ala Pro Leu Trp Gly Pro Pro Pro Ala Gln Gly Ser Pro Gly Asp Gly
180 185 190

Gly Leu Gln Asp Gln Val Gly Ala Trp Gly Leu Pro Gly Pro Thr Gly
195 200 205

Pro Lys Gly Asp Ala Gly Ser Arg Gly Pro Met Gly Met Arg Gly Pro
210 215 220

Pro Gly Pro Gln Gly Pro Pro Gly Ser Pro Gly Arg Ala Gly Ala Val
225 230 235 240

Gly Thr Pro Gly Glu Arg Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly
245 250 255

Pro Pro Gly Pro Pro Ala Pro Val Gly Pro Pro His Ala Arg Ile Ser
260 265 270

Gln His Gly Asp Pro Leu Leu Ser Asn Thr Phe Thr Glu Thr Asn Asn
275 280 285

His Trp Pro Gln Gly Pro Thr Gly Pro Pro Gly Pro Pro Gly Pro Met
290 295 300

Gly Pro Pro Gly Pro Pro Gly Pro Thr Gly Val Pro Gly Ser Pro Gly
305 310 315 320

His Ile Gly Pro Pro Gly Pro Thr Gly Pro Lys Gly Ile Ser Gly His
325 330 335

Pro Gly Glu Lys Gly Glu Arg Gly Leu Arg Gly Glu Pro Gly Pro Gln
340 345 350

Gly Ser Ala Gly Gln Arg Gly Glu Pro Gly Pro Lys Gly Asp Pro Gly
355 360 365

Glu Lys Ser His Trp Asn Gln Ser Trp Gly Leu Gly Gly Pro Cys Arg
370 375 380

His Arg His Pro Gln Pro Pro Ser Gly Gln Glu Gly Gly His Ala Thr
385 390 395 400

Asn Tyr Arg Asp Arg Gly Pro Gln Glu Pro Gly Arg Glu Arg Leu Arg
405 410 415

Val Val Ala Ala Pro Glu Ala Asp Gln Ala Arg Leu Pro Leu Leu Pro
420 425 430

Gly Leu Gly Gln Leu Pro Pro Gly Thr Ala Arg Pro Tyr Leu Leu Met
435 440 445

Ser Ser Gly Ser Leu Leu Pro Ser Arg Pro
450 455

<210> 79
<211> 240
<212> PRT
<213> Homo sapiens

<400> 79
His Ala Ser Ala Ala Arg Ala Ala Ala Gly Ser Glu Pro Arg Thr Gly
1 5 10 15

Cys Gly Gly Ser Ser His Arg Val Pro Leu Gly Pro Ser Pro Ala Ser
20 25 30

Leu Ser Pro Gln Arg Asp Leu Phe Gly Pro Pro Gly Pro Pro Gly Ala
35 40 45

Glu Val Thr Ala Glu Thr Leu Leu His Glu Phe Gln Glu Leu Leu Lys
50 55 60

Glu Ala Thr Glu Arg Arg Phe Ser Gly Leu Leu Asp Pro Leu Leu Pro
65 70 75 80

Gln Gly Ala Gly Leu Arg Leu Val Gly Glu Ala Phe His Cys Arg Leu

85 90 95

Gln Gly Pro Arg Arg Val Asp Lys Arg Thr Leu Val Glu Leu His Gly
100 105 110

Phe Gln Ala Pro Ala Ala Gln Gly Ala Phe Leu Arg Gly Ser Gly Leu
115 120 125

Ser Leu Ala Ser Gly Arg Phe Thr Ala Pro Val Ser Gly Ile Phe Gln
130 135 140

Phe Ser Ala Ser Leu His Val Asp His Ser Glu Leu Gln Gly Lys Ala
145 150 155 160

Arg Leu Arg Ala Arg Asp Val Val Cys Val Leu Ile Cys Ile Glu Ser
165 170 175

Leu Cys Gln Arg His Thr Cys Leu Glu Ala Val Ser Gly Leu Glu Ser
180 185 190

Asn Ser Arg Val Phe Thr Leu Gln Val Gln Gly Leu Leu Gln Leu Gln
195 200 205

Ala Gly Gln Tyr Ala Ser Val Phe Val Asp Asn Gly Ser Gly Ala Val
210 215 220

Leu Thr Ile Gln Ala Gly Ser Ser Phe Ser Gly Leu Leu Leu Gly Thr
225 230 235 240

<210> 80
<211> 256
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (75)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (187)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (229)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (232)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (235)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (236)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
<222> (237)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 80
Met Leu Gly Ala Lys Pro His Trp Leu Pro Gly Pro Leu His Ser Pro
1 5 10 15

Gly Leu Pro Leu Val Leu Val Leu Leu Ala Leu Gly Ala Gly Trp Ala
20 25 30

Gln Glu Gly Ser Glu Pro Val Leu Leu Glu Gly Glu Cys Leu Val Val
35 40 45

Cys Glu Pro Gly Arg Ala Ala Ala Gly Gly Pro Gly Gly Ala Ala Leu
50 55 60

Gly Glu Ala Pro Pro Gly Arg Val Ala Phe Xaa Ala Val Arg Ser His
65 70 75 80

His His Glu Pro Ala Gly Glu Thr Gly Asn Gly Thr Ser Gly Ala Ile
85 90 95

Tyr Phe Asp Gln Val Leu Val Asn Glu Gly Gly Gly Phe Asp Arg Ala
100 105 110

Ser Gly Ser Phe Val Ala Pro Val Arg Gly Val Tyr Ser Phe Arg Phe
115 120 125

His Val Val Lys Val Tyr Asn Arg Gln Thr Val Gln Val Ser Leu Met
130 135 140

Leu Asn Thr Trp Pro Val Ile Ser Ala Phe Ala Asn Asp Pro Asp Val
145 150 155 160

Thr Arg Glu Ala Ala Thr Ser Ser Val Leu Leu Pro Leu Asp Pro Gly
165 170 175

Asp Arg Val Ser Leu Arg Leu Arg Arg Gly Xaa Ser Thr Gly Trp Leu
180 185 190

Glu Ile Leu Lys Phe Leu Trp Leu Pro His Leu Pro Ser Leu Lys Asp
195 200 205

Pro Ser Leu Ser Ser Thr Arg Ile Gln Pro Leu Thr Thr Phe Phe Cys
210 215 220

Pro Leu Leu Pro Xaa Lys Gln Xaa Lys Gln Xaa Xaa Xaa Ser Leu Trp
225 230 235 240

Leu Leu Ser His Leu Phe Ala Trp Glu Pro Val Pro Asn Thr Gln Val
245 250 255

<210> 81
<211> 205
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (80)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (93)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 81
Met Leu Gly Ala Lys Pro His Trp Leu Pro Gly Pro Leu His Ser Pro
1 5 10 15

Gly Leu Pro Leu Val Leu Val Leu Leu Ala Leu Gly Ala Gly Trp Ala
20 25 30

Gln Glu Gly Ser Glu Pro Val Leu Leu Glu Gly Glu Cys Leu Val Val
35 40 45

Cys Glu Pro Gly Arg Ala Ala Ala Gly Gly Pro Gly Gly Ala Ala Leu
50 55 60

Gly Glu Ala Pro Pro Gly Arg Val Ala Phe Ala Ala Val Arg Ser Xaa
65 70 75 80

His His Glu Pro Ala Gly Glu Thr Gly Asn Gly Thr Xaa Gly Ala Ile
85 90 95

Tyr Phe Asp Gln Val Leu Val Asn Glu Gly Gly Gly Phe Asp Arg Ala
100 105 110

Ser Gly Ser Phe Val Ala Pro Val Arg Gly Val Tyr Ser Phe Arg Phe
115 120 125

His Val Val Lys Val Tyr Asn Arg Gln Thr Val Gln Val Ser Leu Met
130 135 140

Leu Asn Thr Trp Pro Val Ile Ser Ala Phe Ala Asn Asp Pro Asp Val
145 150 155 160

Thr Arg Glu Ala Ala Thr Ser Ser Val Leu Leu Pro Leu Asp Pro Gly
165 170 175

Asp Arg Val Ser Leu Arg Leu Arg Arg Gly Asn Leu Leu Gly Gly Trp
180 185 190

Lys Tyr Ser Ser Phe Ser Gly Phe Leu Ile Phe Pro Leu
195 200 205

<210> 82
<211> 180
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (102)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 82
Ala Cys Cys Pro Val Arg Ala Gln Asn Asp Thr Glu Pro Ile Val Leu
1 5 10 15

Glu Gly Lys Cys Leu Val Val Cys Asp Ser Ser Pro Ser Ala Asp Gly
20 25 30

Ala Val Thr Ser Ser Leu Gly Ile Ser Val Arg Ser Gly Ser Ala Lys
35 40 45

Val Ala Phe Ser Ala Thr Arg Ser Thr Asn His Glu Pro Ser Glu Met
50 55 60

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Ser Asn Arg Thr Met Thr Ile Tyr Phe Asp Gln Val Leu Val Asn Ile
 65                 70                  75                  80

Gly Asn His Phe Asp Leu Ala Ser Ser Ile Phe Val Ala Pro Arg Lys
                85                  90                  95

Gly Ile Tyr Ser Phe Xaa Phe His Val Val Lys Val Tyr Asn Arg Gln
            100                 105                 110

Thr Ile Gln Val Ser Leu Met Gln Asn Gly Tyr Pro Val Ile Ser Ala
        115                 120                 125

Phe Ala Gly Asp Gln Asp Val Thr Arg Glu Ala Ala Ser Asn Gly Val
    130                 135                 140

Leu Leu Leu Met Glu Arg Glu Asp Lys Val His Leu Lys Leu Glu Arg
145                 150                 155                 160

Gly Asn Leu Met Gly Gly Trp Lys Tyr Ser Thr Phe Ser Gly Phe Leu
                165                 170                 175

Val Phe Pro Leu
            180



<210> 83
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (62)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (191)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 83
Ala Gly Glu Gly Pro Arg Arg Arg Glu Pro Pro Trp Pro Ala Pro Gln
  1               5                  10                  15

Ile Cys Pro Ala Gly Arg Gly Gly Gly Gly Thr Arg Ala Gly Gly Gly
            20                  25                  30

Ala Gly Arg Ser Ser Gly Arg Gly Gly Glu Gly Tyr Gly Asp Leu Arg
        35                  40                  45

Val Ala Ala Pro Leu Arg Ala Glu Pro Pro Leu Leu Ser Xaa Cys Arg
    50                  55                  60

Pro Ala Tyr Pro Ala Gly Leu Pro Gly Pro Arg Gly Asp Pro Gly Pro
 65                 70                  75                  80

Arg Gly Glu Ala Gly Pro Ala Gly Pro Thr Gly Pro Ala Gly Glu Cys
                85                  90                  95

Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu Ser Arg
            100                 105                 110

Val Pro Pro Pro Ser Asp Ala Pro Leu Pro Phe Asp Arg Val Leu Val
        115                 120                 125

Asn Glu Gln Gly His Tyr Asp Ala Val Thr Gly Lys Phe Thr Cys Gln
```

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    130                 135                 140

Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr Arg Ala
145                 150                 155                 160

Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Glu Ser Ile Ala Ser Phe
                165                 170                 175

Phe Gln Phe Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser Xaa Gly
            180                 185                 190

Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln Val Gly
        195                 200                 205

Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp Ser Thr
    210                 215                 220

Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro Val Phe
225                 230                 235                 240

Ala


<210> 84
<211> 245
<212> PRT
<213> Homo sapiens

<400> 84
Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu
  1               5                  10                  15

Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys
            20                  25                  30

Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp
        35                  40                  45

Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala
    50                  55                  60

Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Leu
 65                  70                  75                  80

Pro Gly His Pro Gly Lys Asn Gly Pro Met Gly Pro Pro Gly Met Pro
                85                  90                  95

Gly Val Pro Gly Pro Met Gly Ile Pro Gly Glu Pro Gly Glu Glu Gly
            100                 105                 110

Arg Tyr Lys Gln Lys Phe Gln Ser Val Phe Thr Val Thr Arg Gln Thr
        115                 120                 125

His Gln Pro Pro Ala Pro Asn Ser Leu Ile Arg Phe Asn Ala Val Leu
    130                 135                 140

Thr Asn Pro Gln Gly Asp Tyr Asp Thr Ser Thr Gly Lys Phe Thr Cys
145                 150                 155                 160

Lys Val Pro Gly Leu Tyr Tyr Phe Val Tyr His Ala Ser His Thr Ala
                165                 170                 175

Asn Leu Cys Val Leu Leu Tyr Arg Ser Gly Val Lys Val Val Thr Phe
            180                 185                 190

Cys Gly His Thr Ser Lys Thr Asn Gln Val Asn Ser Gly Gly Val Leu
```

195 200 205

Leu Arg Leu Gln Val Gly Glu Glu Val Trp Leu Ala Val Asn Asp Tyr
210 215 220

Tyr Asp Met Val Gly Ile Gln Gly Ser Asp Ser Val Phe Ser Gly Phe
225 230 235 240

Leu Leu Phe Pro Asp
245

<210> 85
<211> 76
<212> PRT
<213> Homo sapiens

<400> 85
Ala Leu Pro Arg Leu Gly Arg Ala Asp Ala Leu Glu Thr His Gly Pro
1 5 10 15

Ser Thr Ser Leu Ser Phe Leu His Gly Pro Thr Leu Leu Ala Ser Leu
20 25 30

His Pro Cys Leu Asp His Ser Pro Leu Gln Gly Ala His Pro Asp Pro
35 40 45

Pro Pro Leu His Pro Leu Pro Met Gly Ser Leu Leu Pro Leu Asn Phe
50 55 60

Phe Arg Ser His Cys Leu Cys Gly Ser Trp Asp Thr
65 70 75

<210> 86
<211> 185
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (72)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (86)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (88)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (90)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (109)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
<222> (119)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (148)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (153)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (171)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (172)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (178)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (183)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 86
Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu
1 5 10 15

Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys
20 25 30

Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp
35 40 45

Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Gln Pro
50 55 60

Phe Arg Asp Pro Arg Thr Gln Xaa Ala Glu Gly Arg Thr Arg Leu Thr
65 70 75 80

Arg Pro Ser Trp Glu Xaa Trp Xaa Met Xaa Pro Pro Gly Met Pro Gly
85 90 95

Val Pro Ala His Gly His Pro Trp Arg Ala Gly Glu Xaa Gly Arg Tyr
100 105 110

Lys Gln Lys Phe Gln Ser Xaa Ser Arg His Ser Glu Thr Thr Ala Pro
115 120 125

Asp Pro Thr Ala Asp Arg Ser Thr Arg Ser Asn Asn Arg Arg Arg Tyr
130 135 140

Thr Arg His Xaa Lys Ser Leu Lys Xaa Arg Leu Thr Leu Ala Thr Arg
145 150 155 160

Val Ile Ser Asn Trp Leu Cys Asp Glu Arg Xaa Xaa Gly Thr Leu Gly
165 170 175

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Asn Xaa Asn Ile Gly Asn Xaa Gly Ala
            180                 185


<210> 87
<211> 127
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (127)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 87
Met Phe Val Leu Leu Tyr Val Thr Ser Phe Ala Ile Cys Ala Ser Gly
1               5                   10                  15

Gln Pro Arg Gly Asn Gln Leu Lys Gly Glu Asn Tyr Ser Pro Arg Tyr
            20                  25                  30

Ile Cys Ser Ile Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Ala
        35                  40                  45

Asn Gly Ser Pro Gly Pro His Gly Arg Ile Gly Leu Pro Gly Arg Asp
    50                  55                  60

Gly Arg Asp Gly Arg Lys Gly Glu Lys Gly Glu Lys Gly Thr Ala Gly
65                  70                  75                  80

Leu Arg Gly Lys Thr Gly Pro Leu Gly Leu Ala Gly Glu Lys Gly Asp
                85                  90                  95

Gln Gly Glu Thr Gly Lys Lys Gly Pro Ile Gly Pro Glu Gly Glu Lys
            100                 105                 110

Gly Glu Val Gly Pro Ile Gly Pro Pro Gly Pro Lys Gly Asp Xaa
        115                 120                 125


<210> 88
<211> 285
<212> PRT
<213> Homo sapiens

<400> 88
Met Ile Pro Trp Val Leu Leu Ala Cys Ala Leu Pro Cys Ala Ala Asp
1               5                   10                  15

Pro Leu Leu Gly Ala Phe Ala Arg Arg Asp Phe Arg Lys Gly Ser Pro
            20                  25                  30

Gln Leu Val Cys Ser Leu Pro Gly Pro Gln Gly Pro Pro Gly Pro Pro
        35                  40                  45

Gly Ala Pro Gly Pro Ser Gly Met Met Gly Arg Met Gly Phe Pro Gly
    50                  55                  60

Lys Asp Gly Gln Asp Gly His Asp Gly Asp Arg Gly Asp Ser Gly Glu
65                  70                  75                  80

Glu Gly Pro Pro Gly Arg Thr Gly Asn Arg Gly Lys Pro Gly Pro Lys
                85                  90                  95
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```
Gly Lys Ala Gly Ala Ile Gly Arg Ala Gly Pro Arg Gly Pro Lys Gly
            100                 105                 110

Val Asn Gly Thr Pro Gly Lys His Gly Thr Pro Gly Lys Lys Gly Pro
        115                 120                 125

Lys Gly Lys Lys Gly Glu Pro Gly Leu Pro Gly Pro Cys Ser Cys Gly
    130                 135                 140

Ser Gly His Thr Lys Ser Ala Phe Ser Val Ala Val Thr Lys Ser Tyr
145                 150                 155                 160

Pro Arg Glu Arg Leu Pro Ile Lys Phe Asp Lys Ile Leu Met Asn Glu
                165                 170                 175

Gly Gly His Tyr Asn Ala Ser Ser Gly Lys Phe Val Cys Gly Val Pro
            180                 185                 190

Gly Ile Tyr Tyr Phe Thr Tyr Asp Ile Thr Leu Ala Asn Lys His Leu
        195                 200                 205

Ala Ile Gly Leu Val His Asn Gly Gln Tyr Arg Ile Arg Thr Phe Asp
    210                 215                 220

Ala Asn Thr Gly Asn His Asp Val Ala Ser Gly Ser Thr Ile Leu Ala
225                 230                 235                 240

Leu Lys Gln Gly Asp Glu Val Trp Leu Gln Ile Phe Tyr Ser Glu Gln
                245                 250                 255

Asn Gly Leu Phe Tyr Asp Pro Tyr Trp Thr Asp Ser Leu Phe Thr Gly
            260                 265                 270

Phe Leu Ile Tyr Ala Asp Gln Asp Asp Pro Asn Glu Val
        275                 280                 285


<210> 89
<211> 205
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (5)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (27)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (104)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (119)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 89
Phe Phe Phe Phe Xaa Pro Gly Leu Pro Gly Leu Pro Cys Pro Leu Ser
  1               5                  10                  15
```

```
Ala Leu Leu Ala Glu Ser Arg Arg Ala Arg Xaa Pro Trp Arg Ser Arg
            20                  25                  30

Gly Thr Phe Glu Pro Arg Ala Arg Pro Gly Met His Ala Pro Gly Pro
        35                  40                  45

Pro Gly Leu Phe Ser Gly Pro Gly Leu Thr Val Ala Pro Arg Pro Arg
    50                  55                  60

Gly Pro Ala Gly Gly Gly Gly Glu Val Gly Val His Gln Glu Ala Gly
65                  70                  75                  80

Glu Gly Asp Val Leu Ala Val Val Ala Val Gly Ala Val Ala Val Val
                85                  90                  95

Val Val Ala Glu Gln Pro Glu Xaa Ser Pro Arg Arg Arg Ala Ser Ile
            100                 105                 110

Thr Leu Trp Leu Cys Ile Xaa Ala Ala Pro Arg Arg Ala Val Val Val
        115                 120                 125

Asn His Gly Leu His Leu Val Ala Val Leu His Gln Leu Asn Arg Gln
    130                 135                 140

Arg Leu Thr Arg Gln Leu Ala Gln Arg Glu Gly Glu Glu Val Gly Ala
145                 150                 155                 160

Gly Gln Thr Ala Ala Glu His Ala Gly Arg Arg Val Glu Val Ala Ala
                165                 170                 175

Asn Val Asp Glu Leu Gly Val Glu Gly Glu Trp Leu Val Pro Arg Pro
            180                 185                 190

Gly Pro Ala Ser Glu Pro Thr Lys Leu Arg Ala Leu Cys
        195                 200                 205


<210> 90
<211> 251
<212> PRT
<213> Homo sapiens

<400> 90
Met Lys Ile Pro Trp Gly Ser Ile Pro Val Leu Met Leu Leu Leu Leu
1               5                   10                  15

Leu Gly Leu Ile Asp Ile Ser Gln Ala Gln Leu Ser Cys Thr Gly Pro
            20                  25                  30

Pro Ala Ile Pro Gly Ile Pro Gly Ile Pro Gly Thr Pro Gly Pro Asp
        35                  40                  45

Gly Gln Pro Gly Thr Pro Gly Ile Lys Gly Glu Lys Gly Leu Pro Gly
    50                  55                  60

Leu Ala Gly Asp His Gly Glu Phe Gly Glu Lys Gly Asp Pro Gly Ile
65                  70                  75                  80

Pro Gly Asn Pro Gly Lys Val Gly Pro Lys Gly Pro Met Gly Pro Lys
                85                  90                  95

Gly Gly Pro Gly Ala Pro Gly Ala Pro Gly Pro Lys Gly Glu Ser Gly
            100                 105                 110

Asp Tyr Lys Ala Thr Gln Lys Ile Ala Phe Ser Ala Thr Arg Thr Ile
        115                 120                 125
```

```
Asn Val Pro Leu Arg Arg Asp Gln Thr Ile Arg Phe Asp His Val Ile
    130                 135                 140

Thr Asn Met Asn Asn Asn Tyr Glu Pro Arg Ser Gly Lys Phe Thr Cys
145                 150                 155                 160

Lys Val Pro Gly Leu Tyr Tyr Phe Thr Tyr His Ala Ser Ser Arg Gly
                165                 170                 175

Asn Leu Cys Val Asn Leu Met Arg Gly Arg Glu Arg Ala Gln Lys Val
            180                 185                 190

Val Thr Phe Cys Asp Tyr Ala Tyr Asn Thr Phe Gln Val Thr Thr Gly
        195                 200                 205

Gly Met Val Leu Lys Leu Glu Gln Gly Glu Asn Val Phe Leu Gln Ala
    210                 215                 220

Thr Asp Lys Asn Ser Leu Leu Gly Met Glu Gly Ala Asn Ser Ile Phe
225                 230                 235                 240

Ser Gly Phe Leu Leu Phe Pro Asp Met Glu Ala
                245                 250
```

<210> 91
<211> 168
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (34)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (40)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (44)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (51)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (57)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (62)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (65)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (83)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 91
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Pro Gly Ile Arg Lys Arg Arg Pro Gln Gly Pro His Gly Pro Lys Val
 1               5                  10                  15

Ala Gln Gly Pro Glu Ala Pro Ser Pro Lys Val Asn Arg Glu Thr Gln
            20                  25                  30

Ala Xaa Gln Lys Met Pro Phe Xaa Ala Thr Arg Xaa Ile Asn Val Pro
        35                  40                  45

Leu Arg Xaa Asp Gln Thr Ile Arg Xaa Asp His Val Ile Xaa Asn Met
    50                  55                  60

Xaa Asn Asn Tyr Glu Pro Arg Ser Gly Lys Phe Thr Cys Lys Val Pro
65                  70                  75                  80

Gly Leu Xaa Tyr Phe Thr Tyr His Ala Ser Ser Arg Gly Asn Leu Cys
                85                  90                  95

Val Asn Leu Met Arg Gly Arg Glu Arg Ala Gln Lys Val Val Thr Phe
            100                 105                 110

Cys Asp Tyr Ala Tyr Asn Thr Phe Gln Val Thr Thr Gly Gly Met Val
        115                 120                 125

Leu Lys Leu Glu Gln Gly Glu Asn Val Phe Leu Gln Ala Thr Asp Lys
    130                 135                 140

Asn Ser Leu Leu Gly Met Glu Gly Ala Asn Ser Ile Phe Ser Gly Phe
145                 150                 155                 160

Leu Leu Phe Pro Asp Met Glu Ala
                165
```

<210> 92
<211> 255
<212> PRT
<213> Homo sapiens

<400> 92
```
His Ser Met Met Met Lys Ile Pro Trp Gly Ser Ile Pro Val Leu Met
 1               5                  10                  15

Leu Leu Leu Leu Leu Gly Leu Ile Asp Ile Ser Gln Ala Gln Leu Ser
            20                  25                  30

Cys Thr Gly Pro Pro Ala Ile Pro Gly Ile Pro Gly Ile Pro Gly Thr
        35                  40                  45

Pro Gly Pro Asp Gly Gln Pro Gly Thr Pro Gly Ile Lys Gly Glu Lys
    50                  55                  60

Gly Leu Pro Gly Leu Ala Gly Asp His Gly Glu Phe Gly Glu Lys Gly
65                  70                  75                  80

Asp Pro Gly Ile Pro Gly Asn Pro Gly Lys Val Gly Pro Lys Gly Pro
                85                  90                  95

Met Gly Pro Lys Gly Gly Pro Gly Ala Pro Gly Ala Pro Gly Pro Lys
            100                 105                 110
```

Gly Glu Ser Gly Asp Tyr Lys Ala Thr Gln Lys Ile Ala Phe Ser Ala
        115   120   125

Thr Arg Thr Ile Asn Val Pro Leu Arg Arg Asp Gln Thr Ile Arg Phe
    130   135   140

Asp His Val Ile Thr Asn Met Asn Asn Asn Tyr Glu Pro Arg Ser Gly
145   150   155   160

Lys Phe Thr Cys Lys Val Pro Gly Leu Tyr Tyr Phe Thr Tyr His Ala
                165   170   175

Ser Ser Arg Gly Asn Leu Cys Val Asn Leu Met Arg Gly Arg Glu Arg
            180   185   190

Ala Gln Lys Val Val Thr Phe Cys Asp Tyr Ala Tyr Asn Thr Phe Gln
        195   200   205

Val Thr Thr Gly Gly Met Val Leu Lys Leu Glu Gln Gly Glu Asn Val
    210   215   220

Phe Leu Gln Ala Thr Asp Lys Asn Ser Leu Leu Gly Met Glu Gly Ala
225   230   235   240

Asn Ser Ile Phe Ser Gly Phe Leu Leu Phe Pro Asp Met Glu Ala
                245   250   255

<210> 93
<211> 258
<212> PRT
<213> Homo sapiens

<400> 93
Ala Phe Ala Lys Ser Tyr Leu Gly Asp Thr Ile Glu Gly Thr Pro Ala
1   5   10   15

Gly Thr Gly Pro Glu Phe Pro Gly Arg Pro Thr Arg Pro Val Leu Pro
            20   25   30

Gln Arg Pro Pro Glu Glu Arg Pro Pro Gln Pro Pro Gly Ser Thr Gly
        35   40   45

Val Ile Ala Glu Thr Gly Gln Ala Gly Pro Pro Ala Gly Ala Gly Val
    50   55   60

Ser Gly Arg Gly Leu Pro Arg Gly Val Asp Gly Gln Thr Gly Ser Gly
65   70   75   80

Thr Val Pro Gly Ala Glu Gly Phe Ala Gly Ala Pro Gly Tyr Pro Lys
                85   90   95

Ser Pro Pro Val Ala Ser Pro Gly Ala Pro Val Pro Ser Leu Val Ser
            100   105   110

Phe Ser Ala Gly Leu Thr Gln Lys Pro Phe Pro Ser Asp Gly Gly Val
        115   120   125

Val Leu Phe Asn Lys Val Leu Val Asn Asp Gly Asp Val Tyr Asn Pro
    130   135   140

Ser Thr Gly Val Phe Thr Ala Pro Tyr Asp Gly Arg Tyr Leu Ile Thr
145   150   155   160

Ala Thr Leu Thr Pro Glu Arg Asp Ala Tyr Val Glu Ala Val Leu Ser
                165   170   175

```
Val Ser Asn Ala Ser Val Ala Gln Leu His Thr Ala Gly Tyr Arg Arg
            180                 185                 190

Glu Phe Leu Glu Tyr His Arg Pro Pro Gly Ala Leu His Thr Cys Gly
        195                 200                 205

Gly Pro Gly Ala Phe His Leu Ile Val His Leu Lys Ala Gly Asp Ala
    210                 215                 220

Val Asn Val Val Val Thr Gly Gly Lys Leu Ala His Thr Asp Phe Asp
225                 230                 235                 240

Glu Met Tyr Ser Thr Phe Ser Gly Val Phe Leu Tyr Pro Phe Leu Ser
                245                 250                 255

His Leu




<210> 94
<211> 232
<212> PRT
<213> Homo sapiens

<400> 94
Thr Arg Pro Val Leu Pro Gln Arg Pro Pro Glu Glu Arg Pro Pro Gln
  1               5                  10                  15

Pro Pro Gly Ser Thr Gly Val Ile Ala Glu Thr Gly Gln Ala Gly Pro
            20                  25                  30

Pro Ala Gly Ala Gly Val Ser Gly Arg Gly Leu Pro Arg Gly Val Asp
        35                  40                  45

Gly Gln Thr Gly Ser Gly Thr Val Pro Gly Ala Glu Gly Phe Ala Gly
    50                  55                  60

Ala Pro Gly Tyr Pro Lys Ser Pro Pro Val Ala Ser Pro Gly Ala Pro
 65                  70                  75                  80

Val Pro Ser Leu Val Ser Phe Ser Ala Gly Leu Thr Gln Lys Pro Phe
                85                  90                  95

Pro Ser Asp Gly Gly Val Val Leu Phe Asn Lys Val Leu Val Asn Asp
            100                 105                 110

Gly Asp Val Tyr Asn Pro Ser Thr Gly Val Phe Thr Ala Pro Tyr Asp
        115                 120                 125

Gly Arg Tyr Leu Ile Thr Ala Thr Leu Thr Pro Glu Arg Asp Ala Tyr
    130                 135                 140

Val Glu Ala Val Leu Ser Val Ser Asn Ala Ser Val Ala Gln Leu His
145                 150                 155                 160

Thr Ala Gly Tyr Arg Arg Glu Phe Leu Glu Tyr His Arg Pro Pro Gly
                165                 170                 175

Ala Leu His Thr Cys Gly Gly Pro Gly Ala Phe His Leu Ile Val His
            180                 185                 190

Leu Lys Ala Gly Asp Ala Val Asn Val Val Val Thr Gly Gly Lys Leu
        195                 200                 205

Ala His Thr Asp Phe Asp Glu Met Tyr Ser Thr Phe Ser Gly Val Phe
```

```
    210                 215                 220

Leu Tyr Pro Phe Leu Ser His Leu
225                 230


<210> 95
<211> 98
<212> PRT
<213> Homo sapiens

<400> 95
Met Ala Val Leu Pro Gly Pro Leu Gln Leu Leu Gly Val Leu Leu Thr
  1               5                  10                  15

Ile Ser Leu Ser Ser Ile Arg Leu Ile Gln Ala Gly Ala Tyr Tyr Gly
             20                  25                  30

Ile Lys Pro Leu Pro Pro Gln Ile Pro Pro Gln Met Pro Pro Gln Ile
         35                  40                  45

Pro Gln Tyr Gln Pro Leu Gly Gln Gln Val Pro His Met Pro Leu Ala
     50                  55                  60

Lys Asp Gly Leu Ala Met Gly Lys Glu Met Pro His Leu Gln Tyr Gly
 65                  70                  75                  80

Lys Glu Tyr Pro His Leu Pro Gln Tyr Met Lys Glu Ile Gln Pro Ala
                 85                  90                  95

Val Asp



<210> 96
<211> 542
<212> PRT
<213> Homo sapiens

<400> 96
Met Gln Ala Cys Gly Gln Leu Cys Ser Gly Ala Pro Gly Glu Gln Asp
  1               5                  10                  15

Ser Gln Val Ser Glu Ile Leu Ser Ala Leu Glu Arg Arg Val Leu Asp
             20                  25                  30

Ser Glu Gly Gln Leu Arg Leu Val Gly Ser Gly Leu His Thr Val Glu
         35                  40                  45

Ala Ala Gly Glu Ala Arg Gln Ala Thr Leu Glu Gly Leu Gln Glu Val
     50                  55                  60

Val Gly Arg Leu Gln Asp Arg Val Asp Ala Gln Asp Glu Thr Ala Ala
 65                  70                  75                  80

Glu Phe Thr Leu Arg Leu Asn Leu Thr Ala Ala Arg Leu Gly Gln Leu
                 85                  90                  95

Glu Gly Leu Leu Gln Ala His Gly Asp Glu Gly Cys Gly Ala Cys Gly
            100                 105                 110

Gly Val Gln Glu Glu Leu Gly Arg Leu Arg Asp Gly Val Glu Arg Cys
        115                 120                 125

Ser Cys Pro Leu Leu Pro Pro Arg Gly Pro Gly Ala Gly Pro Gly Val
```

```
    130                 135                 140

Gly Gly Pro Ser Arg Gly Pro Leu Asp Gly Phe Ser Val Phe Gly Gly
145                 150                 155                 160

Ser Ser Gly Ser Ala Leu Gln Ala Leu Gln Gly Glu Leu Ser Glu Val
                165                 170                 175

Ile Leu Ser Phe Ser Ser Leu Asn Asp Ser Leu Asn Glu Leu Gln Thr
            180                 185                 190

Thr Val Glu Gly Gln Gly Ala Asp Leu Ala Asp Leu Gly Ala Thr Lys
        195                 200                 205

Asp Arg Ile Ile Ser Glu Ile Asn Arg Leu Gln Gln Glu Ala Thr Glu
    210                 215                 220

His Ala Thr Glu Ser Glu Glu Arg Phe Arg Gly Leu Glu Glu Gly Gln
225                 230                 235                 240

Ala Gln Ala Gly Gln Cys Pro Ser Leu Glu Gly Arg Leu Gly Arg Leu
                245                 250                 255

Glu Gly Val Cys Glu Arg Leu Asp Thr Val Ala Gly Gly Leu Gln Gly
            260                 265                 270

Leu Arg Glu Gly Leu Ser Arg His Val Ala Gly Leu Trp Ala Gly Leu
        275                 280                 285

Arg Glu Thr Asn Thr Thr Ser Gln Met Gln Ala Ala Leu Leu Glu Lys
    290                 295                 300

Leu Val Gly Gly Gln Ala Gly Leu Gly Arg Arg Leu Gly Ala Leu Asn
305                 310                 315                 320

Ser Ser Leu Gln Leu Leu Glu Asp Arg Leu His Gln Leu Ser Leu Lys
                325                 330                 335

Asp Leu Thr Gly Pro Ala Gly Glu Ala Gly Pro Pro Gly Pro Pro Gly
            340                 345                 350

Leu Gln Gly Pro Pro Gly Pro Ala Gly Pro Pro Gly Ser Pro Gly Lys
        355                 360                 365

Asp Gly Gln Glu Gly Pro Ile Gly Pro Pro Gly Pro Gln Gly Glu Gln
    370                 375                 380

Gly Val Glu Gly Ala Pro Ala Ala Pro Val Pro Gln Val Ala Phe Ser
385                 390                 395                 400

Ala Ala Leu Ser Leu Pro Arg Ser Glu Pro Gly Thr Val Pro Phe Asp
                405                 410                 415

Arg Val Leu Leu Asn Asp Gly Gly Tyr Tyr Asp Pro Glu Thr Gly Val
            420                 425                 430

Phe Thr Ala Pro Leu Ala Gly Arg Tyr Leu Leu Ser Ala Val Leu Thr
        435                 440                 445

Gly His Arg His Glu Lys Val Glu Ala Val Leu Ser Arg Ser Asn Gln
    450                 455                 460

Gly Val Ala Arg Val Asp Ser Gly Gly Tyr Glu Pro Glu Gly Leu Glu
465                 470                 475                 480

Asn Lys Pro Val Ala Glu Ser Gln Pro Ser Pro Gly Thr Leu Gly Val
                485                 490                 495
```

Phe Ser Leu Ile Leu Pro Leu Gln Ala Gly Asp Thr Val Cys Val Asp
500 505 510

Leu Val Met Gly Gln Leu Ala His Ser Glu Glu Pro Leu Thr Ile Phe
515 520 525

Ser Gly Ala Leu Leu Tyr Gly Asp Pro Glu Leu Glu His Ala
530 535 540

<210> 97
<211> 333
<212> PRT
<213> Homo sapiens

<400> 97
Met Arg Ile Trp Trp Leu Leu Leu Ala Ile Glu Ile Cys Thr Gly Asn
1 5 10 15

Ile Asn Ser Gln Asp Thr Cys Arg Gln Gly His Pro Gly Ile Pro Gly
20 25 30

Asn Pro Gly His Asn Gly Leu Pro Gly Arg Asp Gly Arg Asp Gly Ala
35 40 45

Lys Gly Asp Lys Gly Asp Ala Gly Glu Pro Gly Arg Pro Gly Ser Pro
50 55 60

Gly Lys Asp Gly Thr Ser Gly Glu Lys Gly Glu Arg Gly Ala Asp Gly
65 70 75 80

Lys Val Glu Ala Lys Gly Ile Lys Gly Asp Gln Gly Ser Arg Gly Ser
85 90 95

Pro Gly Lys His Gly Pro Lys Gly Leu Ala Gly Pro Met Gly Glu Lys
100 105 110

Gly Leu Arg Gly Glu Thr Gly Pro Gln Gly Gln Lys Gly Asn Lys Gly
115 120 125

Asp Val Gly Pro Thr Gly Pro Glu Gly Pro Arg Gly Asn Ile Gly Pro
130 135 140

Leu Gly Pro Thr Gly Leu Pro Gly Pro Met Gly Pro Ile Gly Lys Pro
145 150 155 160

Gly Pro Lys Gly Glu Ala Gly Pro Thr Gly Pro Gln Gly Glu Pro Gly
165 170 175

Val Arg Gly Ile Arg Gly Trp Lys Gly Asp Arg Gly Glu Lys Gly Lys
180 185 190

Ile Gly Glu Thr Leu Val Leu Pro Lys Ser Ala Phe Thr Val Gly Leu
195 200 205

Thr Val Leu Ser Lys Phe Pro Ser Ser Asp Val Pro Ile Lys Phe Asp
210 215 220

Lys Ile Leu Tyr Asn Glu Phe Asn His Tyr Asp Thr Ala Ala Gly Lys
225 230 235 240

Phe Thr Cys His Ile Ala Gly Val Tyr Tyr Phe Thr Tyr His Ile Thr
245 250 255

Val Phe Ser Arg Asn Val Gln Val Ser Leu Val Lys Asn Gly Val Lys

```
            260                 265                 270

Ile Leu His Thr Lys Asp Ala Tyr Met Ser Ser Glu Asp Gln Ala Ser
        275                 280                 285

Gly Gly Ile Val Leu Gln Leu Lys Leu Gly Asp Glu Val Trp Leu Gln
    290                 295                 300

Val Thr Gly Gly Glu Arg Phe Asn Gly Leu Phe Ala Asp Glu Asp Asp
305                 310                 315                 320

Asp Thr Thr Phe Thr Gly Phe Leu Leu Phe Ser Ser Pro
                325                 330


<210> 98
<211> 159
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (43)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (155)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 98
Gln Glu Gly Ser Glu Pro Val Leu Leu Glu Gly Glu Cys Leu Val Val
  1               5                  10                  15

Cys Glu Pro Gly Arg Ala Ala Ala Gly Gly Pro Gly Gly Ala Ala Leu
             20                  25                  30

Gly Glu Ala Pro Pro Gly Arg Val Ala Phe Xaa Ala Val Arg Ser His
        35                  40                  45

His His Glu Pro Ala Gly Glu Thr Gly Asn Gly Thr Ser Gly Ala Ile
    50                  55                  60

Tyr Phe Asp Gln Val Leu Val Asn Glu Gly Gly Gly Phe Asp Arg Ala
 65                  70                  75                  80

Ser Gly Ser Phe Val Ala Pro Val Arg Gly Val Tyr Ser Phe Arg Phe
                 85                  90                  95

His Val Val Lys Val Tyr Asn Arg Gln Thr Val Gln Val Ser Leu Met
            100                 105                 110

Leu Asn Thr Trp Pro Val Ile Ser Ala Phe Ala Asn Asp Pro Asp Val
        115                 120                 125

Thr Arg Glu Ala Ala Thr Ser Ser Val Leu Leu Pro Leu Asp Pro Gly
    130                 135                 140

Asp Arg Val Ser Leu Arg Leu Arg Arg Gly Xaa Ser Thr Gly Trp
145                 150                 155


<210> 99
<211> 27
<212> DNA
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<213> Homo sapiens

<400> 99
gcggcaagct ttttgcaaag cctaggc 27

<210> 100
<211> 287
<212> PRT
<213> Homo sapiens

<400> 100
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Pro Arg Val Arg Lys Glu Pro Glu Ala Met Gln Trp Leu Arg Val Arg
1               5                   10                  15

Glu Ser Pro Gly Glu Ala Thr Gly His Arg Val Thr Met Gly Thr Ala
            20                  25                  30

Ala Leu Gly Pro Val Trp Ala Ala Leu Leu Leu Phe Leu Leu Met Cys
        35                  40                  45

Glu Ile Pro Met Val Glu Leu Thr Phe Asp Arg Ala Val Ala Ser Asp
    50                  55                  60

Cys Gln Arg Cys Cys Asp Ser Glu Asp Pro Leu Asp Pro Ala His Val
65                  70                  75                  80

Ser Ser Ala Ser Ser Ser Gly Arg Pro His Ala Leu Pro Glu Ile Arg
                85                  90                  95

Pro Tyr Ile Asn Ile Thr Ile Leu Lys Gly Asp Lys Gly Asp Pro Gly
            100                 105                 110

Pro Met Gly Leu Pro Gly Tyr Met Gly Arg Glu Gly Pro Gln Gly Glu
        115                 120                 125

Pro Gly Pro Gln Gly Ser Lys Gly Asp Lys Gly Glu Met Gly Ser Pro
    130                 135                 140

Gly Ala Pro Cys Gln Lys Arg Phe Phe Ala Phe Ser Val Gly Arg Lys
145                 150                 155                 160

Thr Ala Leu His Ser Gly Glu Asp Phe Gln Thr Leu Leu Phe Glu Arg
                165                 170                 175

Val Phe Val Asn Leu Asp Gly Cys Phe Asp Met Ala Thr Gly Gln Phe
            180                 185                 190

Ala Ala Pro Leu Arg Gly Ile Tyr Phe Phe Ser Leu Asn Val His Ser
        195                 200                 205

Trp Asn Tyr Lys Glu Thr Tyr Val His Ile Met His Asn Gln Lys Glu
    210                 215                 220

Ala Val Ile Leu Tyr Ala Gln Pro Ser Glu Arg Ser Ile Met Gln Ser
225                 230                 235                 240

Gln Ser Val Met Leu Asp Leu Ala Tyr Gly Asp Arg Val Trp Val Arg
                245                 250                 255

Leu Phe Lys Arg Gln Arg Glu Asn Ala Ile Tyr Ser Asn Asp Phe Asp
            260                 265                 270

Thr Tyr Ile Thr Phe Ser Gly His Leu Ile Lys Ala Glu Asp Asp
        275                 280                 285
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<210> 101
<211> 162
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (1)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (33)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (48)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 101
Xaa Leu Trp Asp Pro Gly Leu Pro Gly Val Cys Arg Cys Gly Ser Ile
1 5 10 15

Val Leu Lys Ser Ala Phe Ser Val Gly Ile Thr Thr Ser Tyr Pro Glu
20 25 30

Xaa Arg Leu Pro Ile Ile Phe Asn Lys Val Leu Leu Pro Arg Gly Xaa
35 40 45

Ala Leu Gln Pro Cys His Arg Gly Ser Ser Ser Val Leu Ser Gln Gly
50 55 60

Ile Tyr Tyr Phe Ser Tyr Asp Ile Thr Leu Ala Asn Lys His Leu Ala
65 70 75 80

Ile Gly Leu Val His Asn Gly Gln Tyr Arg Ile Lys Thr Phe Asp Ala
85 90 95

Asn Thr Gly Asn His Asp Val Ala Ser Gly Ser Thr Val Ile Tyr Leu
100 105 110

Gln Pro Glu Asp Glu Val Trp Leu Glu Ile Phe Phe Thr Asp Gln Asn
115 120 125

Gly Leu Phe Ser Asp Pro Gly Trp Ala Asp Ser Leu Phe Ser Gly Phe
130 135 140

Leu Leu Tyr Val Asp Thr Asp Tyr Leu Asp Ser Ile Ser Glu Asp Asp
145 150 155 160

Glu Leu

<210> 102
<211> 15
<212> PRT
<213> Homo sapiens

<400> 102
Gly Ser Ile Val Leu Lys Ser Ala Phe Ser Val Gly Ile Thr Thr
1 5 10 15

<210> 103
<211> 14
<212> PRT
<213> Homo sapiens

<400> 103
Gly Ile Tyr Tyr Phe Ser Tyr Asp Ile Thr Leu Ala Asn Lys
1 5 10

<210> 104
<211> 13
<212> PRT
<213> Homo sapiens

<400> 104
Asp Ser Leu Phe Ser Gly Phe Leu Leu Tyr Val Asp Thr
1 5 10

<210> 105
<211> 13
<212> PRT
<213> Homo sapiens

<400> 105
Asn His Asp Val Ala Ser Gly Ser Thr Val Ile Tyr Leu
1 5 10

<210> 106
<211> 126
<212> PRT
<213> Homo sapiens

<400> 106
Ser Ala Phe Thr Val Ile Leu Ser Lys Ala Tyr Pro Ala Val Gly Ala
1 5 10 15

Pro Ile Pro Phe Asp Glu Ile Leu Tyr Asn Arg Gln Gln His Tyr Asp
20 25 30

Pro Arg Ser Gly Ile Phe Thr Cys Lys Ile Pro Gly Ile Tyr Tyr Phe
35 40 45

Ser Tyr His Ile His Val Lys Gly Thr His Val Trp Val Gly Leu Tyr
50 55 60

Lys Asn Gly Thr Pro Thr Met Tyr Thr Tyr Asp Glu Tyr Ser Lys Gly
65 70 75 80

Tyr Leu Asp Gln Ala Ser Gly Ser Ala Ile Met Glu Leu Thr Glu Asn
85 90 95

Asp Gln Val Trp Leu Gln Leu Pro Asn Ala Glu Ser Asn Gly Leu Tyr
100 105 110

Ser Ser Glu Tyr Val His Ser Ser Phe Ser Gly Phe Leu Val
115 120 125

<210> 107
<211> 126

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<212> PRT
<213> Homo sapiens

<400> 107
Ser Ala Phe Ser Val Ala Val Thr Lys Ser Tyr Pro Arg Glu Arg Leu
 1               5                  10                  15

Pro Ile Lys Phe Asp Lys Ile Leu Met Asn Glu Gly Gly His Tyr Asn
            20                  25                  30

Ala Ser Ser Gly Lys Phe Val Cys Gly Val Pro Gly Ile Tyr Tyr Phe
        35                  40                  45

Thr Tyr Asp Ile Thr Leu Ala Asn Lys His Leu Ala Ile Gly Leu Val
    50                  55                  60

His Asn Gly Gln Tyr Arg Ile Arg Thr Phe Asp Ala Asn Thr Gly Asn
65                  70                  75                  80

His Asp Val Ala Ser Gly Ser Thr Ile Leu Ala Leu Lys Gln Gly Asp
                85                  90                  95

Glu Val Trp Leu Gln Ile Phe Tyr Ser Glu Gln Asn Gly Leu Phe Tyr
            100                 105                 110

Asp Pro Tyr Trp Thr Asp Ser Leu Phe Thr Gly Phe Leu Ile
        115                 120                 125
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